University of Alberta

Dietary Patterns and Chemosensory Perception in Patients with Advanced Cancer

by

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ABSTRACT

Dietary Patterns and Chemosensory Perception in Patients with Advanced Cancer

Current nutrition intervention strategies for patients with advanced cancer are not developed in the context of dietary intake, chemosensory limitations or food preferences. This research was conducted to characterize the current dietary intake and to examine the relationship between self-perceived chemosensory impairment, food intake and quality of life in patients with advanced cancer. Subjects (n=114) completed a 3-day dietary record to estimate nutrient intake and dietary patterns. Self-perceived chemosensory function and quality of life were assessed by way of questionnaire (n=50). Wide variation in estimated energy (25.3 ± 10 kcal/kg/day, mean ± SD) and protein (1.0 ± 0.4 g/kg/day) intakes were observed; low intakes were associated with decreased frequency of eating, limited dietary variety, and self-perceived chemosensory dysfunction. Acute chemosensory complaints were associated with decreased food enjoyment (*P*=.0110) and quality of life (*P*=.0070). These results describe current food selection and nutrient intake in patients with advanced cancer and highlight the importance of recognizing the current dietary habits, food preferences and sensory symptomology of this patient group when developing a nutrition intervention.

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LIST OF ABBREVIATIONS

3-AFC:	3-choice alternative forced choice ascending series of limits
A/CS:	Anorexia/cachexia nutritional related well-being
AIDS:	Acquired Immune Deficiency Syndrome
ANOVA:	Analysis of variance
ASTM:	American Society for Testing and Materials
BMI:	Body mass index (weight[kg]/height[m^2])
BMR:	Basal metabolic rate
BUN:	Blood urea nitrogen
BW:	body weight (kg)
DLW:	Doubly-labeled water
EAR:	Estimated Average Requirement
ESAS:	Edmonton Symptom Assessment Scale
EWB:	Emotional well-being
FAACT:	Functional Assessment of Anorexia/Cachexia Therapy©
FFM:	Fat free mass
FFQ:	Food frequency questionnaire
FWB:	Functional well-being
g:	gram
HIV:	Human Immunodeficiency Virus
ISO:	International Organization for Standardization
kcal:	kilocalorie
kg:	kilogram

ml:	milliliters
NS:	Not significant at $\alpha=0.05$
NSCLC:	Non-small cell lung cancer
PWB:	Physical well-being
QOL:	Quality of life
RDA:	Recommended Dietary Allowance
REE:	Resting energy expenditure
RMR:	Resting metabolic rate
SD:	Standard deviation
SEM:	Standard error of the mean
SFWB:	Social/family well-being
TEE:	Total energy expenditure
TEF:	Thermic effect of food
TNF-α:	Tumor Necrosis Factor alpha

CHAPTER ONE

1.1 INTRODUCTION

The National Cancer Institute of Canada estimates that 145,500 Canadians, including 13,100 Albertans, will be newly diagnosed with cancer in 2004[1]. Cancer is primarily a disease of the elderly; greater than 69% of all new cases and 80% of cancer deaths occur in individuals who are at least 60 years old[1]. As the Canadian population continues to age and increase in size, the number of cancer deaths will continue to rise; it is projected that 68,300 Canadians (including 5,300 Albertans) will die from cancer in 2004[1].

When an individual is diagnosed with cancer, curative therapies such as chemotherapy or radiation are initiated and control of the disease is aggressively pursued until it becomes apparent that a complete recovery is not possible. At this point, therapeutic goals switch focus from an intent to cure to prolongation of life and palliation of symptoms. Some individuals may be diagnosed with cancer at an advanced stage and enter palliative care upon diagnosis. Throughout this disease trajectory, malnutrition and cancer develop progressively, culminating in a state of severe depletion and unique nutritional concerns. As a result, malnutrition is highly prevalent among patients with advanced cancer and is estimated to occur in 40 to 90% of patients[2] depending on tumor type, disease stage and treatment regimen[3].

The malnutrition associated with advanced neoplastic disease is a multifactorial problem. Decreased appetite resulting in inadequate dietary intake is an important contributor to the weight loss and progressive functional decline associated with advanced disease. Anorexia is the most consistent clinical finding in weight-losing cancer patients[4]; the anorexia, weight loss, and impaired nutritional status related to decreased dietary intake are associated with poorer prognosis[5-7] and diminished quality of life[8,9] in patients with advanced cancer. For these reasons, the development of nutrition interventions and other therapeutic strategies targeting malnutrition in this population has become a priority among researchers.

The anorexia associated with malignancy may be related in part to changes in taste perception, which can lead to a general reduction in the pleasurable aspect of taste and a reduction in food palatability, resulting in an overall decline in appetite and an impaired nutritional intake. Research in other patient populations has demonstrated that chemosensory losses and distortions are strongly associated with nutritional status[10,11], food enjoyment[9,11] and quality of life[9,12]. An increased understanding of the relationship between abnormal chemosensory function and dietary behavior in patients with advanced cancer may lead to improved management and palliation of this symptom, and ultimately improved nutritional status in this population.

1.2 RATIONALE

It is standard dietetic practice to consider a patient's requirements along with dietary habits and preferences when planning nutrition intervention and providing dietary recommendations. However, existing practice and investigational strategies targeting the malnutrition of advanced cancer are restricted by the limited knowledge of specific nutrient requirements and current food and nutrient intakes for this population. Information relating to current nutrient intakes and food preferences, and an increased understanding of the effects of chemosensory symptomology on nutrient intake, are required to develop suitable dietary interventions that optimize nutritional status in patients with advanced cancer.

1.3 HYPOTHESES

This research was undertaken to explore the following hypotheses:

A. Patients with advanced cancer will stratify into distinct dietary patterns that will be determinants of nutrient intake.

B. A large proportion of palliative patients with advanced cancer experience self-perceived taste and smell alterations;

C. Self-perceived abnormalities of chemosensory function relate significantly to low nutrient intake and perceived quality of life in patients with advanced cancer.

1.4 OBJECTIVES

This research was conducted to increase current knowledge regarding nutrient intakes and dietary habits among patients with advanced cancer, and to explore the relationship between chemosensory function, food intake and quality of life in this population.

The specific objectives were:

A. To describe food and nutrient intakes and identify dietary patterns in a population of palliative patients with advanced cancer.

B. To explore the relationship between dietary pattern and nutrient intake.

C. To determine the prevalence of taste and smell alterations in palliative patients with advanced cancer.

D. To determine if there is a relationship between self-perceived taste and smell capabilities, nutrient/food intake, and food enjoyment as a component of quality of life.

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CHAPTER TWO

2.0 DIETARY ASSESSMENT IN PATIENTS WITH ADVANCED CANCER: NUTRIENT REQUIREMENTS, NUTRIENT INTAKES AND DIETARY PATTERNS

There are significant limitations in the current knowledge of general nutrition for patients with advanced cancer. The current dietary recommendations and nutritional interventions for patients with advanced cancer are, at best, crude estimates and are not based on a comprehensive understanding of nutrient requirements determined using standardized objective measures. Furthermore, the typical nutrient intakes and food choices for individuals with advanced cancer are not well documented. Due to small patient numbers and narrowly defined patient groups, the dietary information reported for patients with advanced cancer cannot be considered representative of the population and therefore may be of limited value in clinical practice.

This review will focus primarily on the nutritional deficits associated with advanced cancer. The current literature relating to appetite, dietary intake, and energy and nutrient requirements in patients with advanced cancer will be explored and limitations in current knowledge and clinical practice will be highlighted. Basic principles of measuring energy and nutrient requirements and dietary intakes will be discussed with an emphasis on their application in advanced cancer populations.

2.1 NUTRIENT REQUIREMENTS IN CANCER

While it is generally assumed that tumor type, disease progression, abnormal metabolic processes and standard treatment protocols would alter nutrient requirements[1,2], the effects of cancer progression on specific nutrient requirements have not been systematically measured in large-scale investigations. While measurements of energy expenditure have provided information relating to energy requirements in patients with advanced cancer, there is a limited understanding of specific dietary requirements for most nutrients.

2.1.1 COMPONENTS OF ENERGY EXPENDITURE

The amount of energy used or required to support the metabolic activity of cells, maintain normal function of organs and organ systems, and to perform physical work in a 24-hour period is referred to as total energy expenditure (TEE). The primary components of TEE include the basal or resting metabolic rate (BMR or RMR), the thermic effect of food (TEF), and physical activity.

BMR is the energy expended to support essential body functions in the postabsorptive and relaxed state, measured under comfortable environmental and thermal conditions with the individual in a supine position. BMR, usually measured over a 30- or 60-minute period, is typically extrapolated to reflect 24-hour expenditures, and is referred to as basal energy expenditure (BEE). Resting energy expenditure (REE) is an estimate of basal metabolism measured under similar conditions; however, the subject is not required to be in the post-absorptive state. Basal metabolism is highly correlated with fat free mass (FFM), which accounts for approximately 70 to 80% of variance in REE[3]. Age, gender, nutritional status, body composition and genetics are additional factors affecting REE[4].

The energy expended by physical activity is the most variable component of TEE as it depends on the type, intensity, duration and frequency of the activity that one engages in. TEF is the increased energy expenditure due to the energy costs associated with digestion, absorption and metabolism of ingested nutrients[5].

2.1.2 *MEASURING ENERGY EXPENDITURE*

The measurement of energy expenditure depends on the principle that all the energy used by the body will ultimately appear as heat. The body's ability to derive energy from food is due to the chemical oxidation of macronutrients, which requires a supply of oxygen. Direct calorimetry, which measures the heat produced by the body, is a precise method that can be used to determine energy expenditure under laboratory conditions[6]. Though direct calorimetry is considered the gold standard for measuring energy expenditure, this method is expensive and is of limited practicality given new methods of measuring energy expenditure. To date, direct calorimetry has not been used to estimate energy expenditure in patients with advanced cancer.

The measurement of oxygen consumption and CO_2 production by indirect calorimetry provides the most commonly used estimate of the energy or heat produced by these oxidative processes, and is therefore a measure of energy expenditure[6,7]. Indirect calorimetry is commonly used to measure basal metabolism; values are typically reported in the literature as REE.

The doubly-labeled water (DLW) method is now widely used to measure TEE in human subjects[8]. The subject is given water enriched with ^2H_2O and $H_2{}^{18}O$; by measuring the disappearance of these isotopes from the body, one can estimate CO_2 production. This value is used to calculate estimates of heat production, provided that the macromolecular composition of the foods consumed and oxidized is known, as this governs the amount of energy released per liter of CO_2 produced. One of the major benefits of the DLW method is that it allows measurement of energy metabolism by unrestrained humans performing their usual activities in their normal environments. To date, both indirect calorimetry and DLW have been used to measure energy expenditure in patients with advanced cancer[9-17].

2.1.3 ENERGY REQUIREMENTS IN PATIENTS WITH CANCER

The energy requirements of an individual are defined on the basis of current body composition and specific goals for energy balance[18]. For example, for an individual with a desirable and healthy body weight, energy intake must match TEE to maintain energy balance. However, for an underweight individual, energy requirements and ideally energy intake would exceed expenditure, establishing a positive energy balance and allowing for weight gain. In the clinical setting, estimates of individual energy requirements typically begin with a measurement or calculation of predicted basal or resting energy expenditure[7,8,19-23]. Values are then multiplied by a coefficient of physical activity and/or a stress or injury factor depending on estimated levels of physical activity[24] and energy cost of the pathophysiological state.

The effects of malignancy on basal metabolic rate have been investigated in various cancer populations with results ranging from hypo- to hypermetabolism. In a study of over 200 heterogeneous malnourished cancer patients, Knox et al[15] measured basal energy expenditure by indirect calorimetry and compared measured values to those predicted using the Harris-Benedict equation[20]. Patients were considered hypermetabolic if measured metabolic rate was >110% of the predicted value and hypometabolic if measured metabolic rate was <90% of predicted. The researchers found that 33% of patients studied had a decreased metabolic rate, 26% had an increased metabolic rate and 41% had a normal metabolic rate relative to predicted values. Results indicated that hypermetabolic patients had a significantly longer duration of disease

(32.8 months) than the normometabolic patients (12.8 months). This suggests that the duration and/or stage of development of malignancy play an important role in energy metabolism, a concept that has been supported by longitudinal studies of energy metabolism using animal tumor models[25]. Tumor-type and primary site have also been implicated as factors in abnormal energy expenditure[19,26].

Bosaeus et al[10] used indirect calorimetry to compare measured metabolic rate to predicted values (calculated using Harris-Benedict equation[20]), dietary intake and weight loss for 297 patients with generalized malignant disease of solid tumor type. Over 48% of patients were classified as hypermetabolic, with a measured metabolic rate > 110% of predicted. Underweight patients had a significantly higher metabolic rate than those who were overweight, and weight losing patients had a higher metabolic rate than weight-stable or weight-gaining patients. Taking a different approach, Hyltander et al[13] classified cancer patients and healthy controls into weight-losing and weight-stable groups and found that cancer patients had significantly higher metabolic rate compared to both weight-stable and weight-losing controls.

Jatoi et al[14] measured basal metabolism in patients with non-small cell lung cancer (NSCLC) and expressed metabolic rate as a function of lean body mass. Unadjusted measured metabolic rate was not different than healthy controls, however, when adjusted for lean body mass resting metabolic rate was significantly higher in patients with NSCLC. Similarly, patients with advanced pancreatic cancer were shown to have a significantly higher resting metabolic rate per unit of lean body mass relative to healthy age-matched controls[11].

Though there is wide variation in the measured metabolic rate of cancer patients, the bulk of evidence derived from indirect calorimetry suggests that increased basal metabolic rate is present in a significant proportion of cancer patients and is most common among patients who have lost weight[17]. This would indicate that basal energy requirements are significantly increased relative to healthy controls; however, decreased physical activity related to inadequate dietary intake, fatigue and other symptoms may result in a net reduction or maintenance of TEE.

DLW has been used to determine TEE and estimate energy requirements in healthy weight-stable individuals[8], based on the assumption that for an individual with a desirable and healthy body weight, energy intake must match TEE to maintain energy balance. However, patients with advanced cancer are often not in energy balance, as demonstrated by the profound weight loss observed in this population[27-29]; there are limitations to the use of the DLW method for estimating energy requirements in underfed individuals.

In a recent study[16], basal energy metabolism and TEE were measured in weight-losing pancreatic cancer patients. While a significantly increased basal metabolic rate was observed (compared to that predicted using Schofield's equation[30]), TEE was significantly lower than predicted (predicted TEE = predicted basal metabolic rate x 1.5) due to decreased energy expenditure of activity[16]. The mean measured TEE was approximately 1.25 times greater than measured basal metabolism, indicating a physical activity level comparable to chair-bound sedentary individuals and inconsistent with even low levels of physical activity[24]. This suggests that for some patients with elevated resting metabolic rate, TEE may be unchanged despite increased basal energy expenditure, due to compensatory energy-sparing behavior[12,16]. Furthermore, Moses et al[16] provided direct evidence that increased caloric intake was partitioned to increased physical activity levels and not tissue accrual in patients receiving an eicosapentanoic-enriched dietary supplement; these results suggest a relationship between the low activity levels and inadequate dietary intake. If in fact, the low TEE is in part an adaptive strategy to minimize an energy deficit created by elevated resting metabolism and inadequate dietary intake, TEE measured by DLW may not be an appropriate measure of true energy requirement in this population.

It would be most accurate to determine the specific energy requirements of each patient by measuring individual metabolic rates. Where this is not clinically feasible, the validity of estimates used in clinical practice must be considered. Bauer et al[9] assessed the agreement between basal metabolism measured with indirect calorimetry in pancreatic cancer patients and that estimated using various prediction equations (including the Harris-Benedict[20], Mifflin-St.Jeor[21], Owen[22,23], Schofield[30], Cunningham[31], and Wang[32] equations and the 20kcal/kg BW ratio). They found that the Harris-Benedict[20] equation demonstrated the best agreement at the individual level, and suggest its use for pancreatic cancer patients. The authors note that the Harris-Benedict equation has been found to overestimate basal metabolic rate by 5 to 15% in healthy populations[19,21-23]; perhaps its apparent suitability for use with cancer patients supports findings of hypermetabolism in this patient population.

Measurements of basal metabolism comprise at least a starting point for further calculations approximating a patient or population's total energy requirements. The mean resting metabolic rate of cancer patients with various diagnoses has been measured to fall between 22.0kcal/kg BW/day and 23.6kcal/kg BW/day[10-13]. Various multipliers of basal metabolism are used to estimate total energy requirements; for use in clinical practice, multiplier values in the range of 1.2 to 1.3 times the basal metabolic rate have been suggested for weight maintenance in patients with cancer[33]. Interestingly, when applied to measured mean values of resting metabolism, these multipliers would correspond to the 25 to 30kcal/kg BW/day range of maintenance energy recommendations used in clinical practice[33-35]. Though these multipliers and recommended energy intake ranges are widely used in clinical practice for patients with advanced cancer, there is evidence to suggest that they underestimate energy requirements for weight maintenance in this population by a wide margin[10,16,36,37].

Ravasco et al[38] used the 1.2 multiplier to estimate energy requirements in 170 patients diagnosed with stage III or IV solid tumors of the gastrointestinal tract. Though energy intakes corresponded to the estimated requirements, all patients reported weight losses greater than 10% usual body weight. Furthermore, if we apply the 1.2 to 1.3 multipliers to estimate total energy requirements for advanced cancer patients, the absolute minimum estimated mean energy requirements would be in the range of 26kcal/kg BW/day (22kcal/kg BW/day x 1.2). In patients with advanced pancreatic cancer, energy intakes of approximately 26kcal/kg BW/day were associated with a rate of weight loss of 5% body weight/month, clearly suggesting an inadequate energy intake[36]. Bosaeus et al[10] observed continued weight loss in 127 advanced cancer patients consuming, on average, 28kcal/kg/day. Similar energy intakes corresponded to negative energy balance among 309 patients with mixed malignancies reporting a mean weight loss of 10% body weight and consuming, on average, 26kcal/kg BW/day[37]. Furthermore, the researchers observed no weight gain in a subset of patients consuming 34kcal/kg BW/day (which would be consistent with a multiplier of 1.54), suggesting energy intakes at or near requirements for weight maintenance. While there is not nearly sufficient information in this area, it would seem highly likely that mean energy requirements to support weight maintenance and minimal levels of physical activity would be in the ballpark of 34kcal/kg, or 1.54 times the basal metabolic rate; requirements for weight gain would be equal to or greater than 35kcal/kg BW/day in patients with advanced malignancy.

2.1.4 DETERMINING PROTEIN AND AMINO ACID REQUIREMENTS

There are various methods to determine protein and amino acid requirements in healthy populations, of which the nitrogen balance (N-balance) method has been most widely used. However, dietary protein and amino acid requirements of cancer patients have never been formally determined, and it has been argued that this is an important deficit in current knowledge[39]. Methods for the determination of human protein requirements continue to advance conceptually and technically, and the subset of these which are minimally invasive merit particular scrutiny for use, since patients with advanced malignancy may not tolerate extensive or invasive investigations. MacKenzie and Baracos[39] suggest that the indicator amino acid oxidation approach may be particularly appropriate since it is suited to vulnerable populations such as premature neonates and children[40,41]. These authors have also suggested that the plasma amino acid response to an infusion of an amino acid mixture may be useful. This method is based on the differential behavior of infused amino acids depending on whether the infusion over-supplies or under-supplies amino acids relative to requirements.

2.1.5 PROTEIN AND AMINO ACID REQUIREMENTS IN PATIENTS WITH CANCER

Given that specific protein and amino acid requirements have not been empirically determined for patients with advanced cancer, a suitable reference point in estimating requirements would be the suggested protein requirements of healthy persons in the range of ages of the average cancer diagnosis (65 years in Canada)[42] and average cancer death (69 years)[42]. The cancer diagnosis and related factors that may alter protein requirements are then considered relative to this baseline requirement value; protein requirements are generally considered to be increased in patients with advanced cancer relative to healthy individuals[39].

A meta-analysis including data from 19 separate N-balance studies was performed to assess the protein requirements of healthy adults[43]. The results of this meta-analysis were used to establish the Dietary Reference Intakes[4] for protein for healthy individuals aged 51 years and older. The [1]Estimated Average Requirement (EAR) and [2]Recommended Dietary Allowance (RDA) for protein for healthy adult men and women are 0.66g and 0.80g protein/kg BW/day, respectively[4]. The RDA is used in practice as the goal for minimum average daily protein intake for healthy adults to ensure that one is at low risk for deficiency.

The RDA value should be considered a minimum amount for patients with cancer for the following reasons. The adequacy of the RDA is based on the assumption that ingested protein is of high biological value and is accompanied by sufficient non-protein energy to prevent oxidation of ingested amino acids; energy intakes among patients with advanced cancer often fall short of requirements and dietary protein is therefore likely to be sacrificed to provide energy. In such a case, protein intakes must exceed this minimum requirement. Furthermore, based on an understanding that there is elevated metabolism and catabolism of amino acids in patients with advanced cancer[44,45], protein requirements are likely to be increased in patients with cancer. Therefore, protein intakes ranging from at least 1.0g/kg BW/day to 2.0g/kg BW/day would be recommended for patients with advanced neoplastic disease[33-35]. Protein intakes as high as 2.0g/kg BW/day have generally been recommended for critically ill, malnourished underweight patients to achieve positive nitrogen balance[35].

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[1] The Estimated Average Requirement (EAR) of a nutrient is the average daily intake value at which one half of the healthy individuals in a defined age and gender group will meet their requirements for that nutrient[4]

[2] The Recommended Dietary Allowance (RDA) of a nutrient is the average daily intake value at which 97 to 98 percent of the healthy individuals in a defined age and gender group will meet their requirements for that nutrient[4]

These values constitute a 'best guess' estimate based on clinical practice and an understanding that protein requirements are likely to be increased in patients with advanced neoplastic disease relative to healthy individuals. However, the range of estimated protein requirement for this population is broad and empirical determinations of requirements are required to support current hypotheses.

It seems clear that protein requirements and those of different specific amino acids are altered by cancer. MacKenzie and Baracos[39] have recently reviewed amino acid utilization and amino acid requirements in the tumor bearing state, drawing upon the available literature from animal models and clinical studies. Changes in metabolism of amino acids are not fully described; however several amino acids appear to show characteristic patterns of utilization, including aromatic, sulfur-containing and branched chain amino acids, as well as the non-essential amino acids alanine, glutamine, cysteine and arginine. Trials of dietary supplementation have been done more extensively for several individual amino acids in laboratory animal models, and from these we can infer the presence of possible amino acid deficiencies characteristic of the tumor bearing state; few amino acid supplementation trials have been done on cancer patients.

Though basal energy requirements for patients with advanced cancer have been extensively studied, the relationship between resting metabolic rate and total energy expenditure remains unclear. The bulk of the evidence suggests that resting metabolic rate is increased, with a minimum mean requirement for weight maintenance of 34kcal/kg BW/day; requirements for tissue accrual are likely to be upwards of 35kcal/kg BW/day[16,37]. Protein requirements are thought to be increased relative to healthy adults due to increased protein turnover, and a unique amino acid requirement profile to prevent lean tissue losses and support tissue accrual is proposed. Empirically derived measures of nutrient requirements are necessary to set appropriate nutrient intake goals and to develop recommendations and nutritional therapies to improve nutritional status and quality of life in patients with advanced cancer.

2.2 NUTRIENT INTAKES IN PATIENTS WITH CANCER

A comparison between current nutrient intakes and dietary requirements is an essential starting point to any dietetic therapy, however, typical nutrient intakes and food choices for individuals with advanced cancer are not well documented. The reported dietary information cannot be considered representative of the advanced cancer population as there have been very few studies, and the majority of these were conducted with small patient numbers and narrowly defined patient groups[16,36,46-48]. Furthermore, many of the studies related to dietary intake in patients with cancer focus on the effects of curative therapies such as chemotherapy, radiation or surgery[49,50]. Therefore, the applicability of the available information to clinical practice can be ambiguous, especially for patients with advanced cancer who are no longer receiving aggressive anti-tumor therapies.

2.2.1 ESTIMATING ENERGY AND NUTRIENT INTAKES

The most common research methods used in determining usual dietary intakes and dietary exposures include the 24-hour recall, dietary record and food frequency questionnaire (FFQ). The decision as to which methodology will be used in a given study generally depends on the research goals and resources available. In addition, one must consider the capabilities of the population under study, as well as the frequency of consumption of the dietary components to be measured. With these considerations in mind, the strengths and limitations of each method must be evaluated to ensure the most appropriate tool is chosen.

The FFQ is used to generate estimates of usual dietary intake. Participants are asked to provide an estimate of their frequency of intake of specific food items over a defined period of time. The FFQ can be modified to suit the needs of a particular study, for example, by including a greater number of foods that are sources of the specific nutrients of interest[51]. FFQs may be especially useful for retrospective studies examining the relationship between disease and previous or long-term dietary exposures. Additional benefits of the FFQ include its relatively low cost and ease of administration, and the ability to assess intake over an extended period of time[51]. However, this method is also susceptible to recall errors and has shown high variability in reporting accuracy when validated using DLW[52,53].

The 24-hour recall method is a nutrition assessment tool often used to estimate current dietary intake. Subjects are prompted to report the foods, beverages and supplements consumed during the previous 24-hour period. Using food models or pictures, measuring tools and standard household items the interviewer collects information regarding the types of foods ingested, cooking methods, ingredients used, brand names, serving sizes and mealtimes. This retrospective method has a relatively low subject burden relative to the food record, however, the accuracy of information gathered is highly dependent on the subject's recall capabilities. Therefore, this approach may not be appropriate for elderly individuals[54].

The prospective dietary record is also commonly used to estimate the current dietary intake of individuals and groups. Subjects are asked to document all foods and beverages consumed during the recording period which typically spans 1 to 7 days. A designated care-giver or researcher may observe meals and record dietary intake for participants who are unable to independently document the information. As with the 24-hour recall, the dietary information collected includes cooking methods, ingredients, brand names, portion sizes, and meal times. Subjects are also encouraged to record the dietary information at the time the foods are consumed, or shortly after. The prospective nature of the food record minimizes recall errors[51]. However, food records may be of limited value in measuring long-term habitual intake because they collect information over a defined and limited number of days[55]. While the collection of 7 to 14-day records may provide a better estimate of usual intake in the healthy population[56], the high subject burden and extended time period make this method unsuitable for patients with advanced cancer. Bruera et al[57] evaluated the reliability of the 24-hour food record in patients with advanced cancer and found good correlation with actual energy and protein intake, thus demonstrating the adequacy of food records for documenting intakes in this population. Three-day dietary food records have been used to estimate energy and protein intakes in patients with advanced cancer[16, 36,58,59].

Dietary intakes estimated via 24-hour recall and diet records frequently demonstrate a bias towards underreporting of energy and protein intakes, especially among women[60-64] and overweight individuals[55,62,63,65]. It remains to be determined whether or to what extent patients affected by wasting syndromes distort dietary records, though the possibility of systematic overestimation of food consumption has been suggested[16]. Cognitive impairment or pressing symptomatic concerns (ie breakthrough pain) may potentially influence the accuracy of food records collected from patients with terminal cancer. Additional potential sources of bias include recall error, incomplete dietary recording, and systematic underreporting of foods considered unhealthy[64, 66]. Nonetheless, these methods are considered to adequately reflect current dietary intake[57,67] and provide reasonable estimates of mean group dietary intake[68], and are often used to validate other methodologies for dietary intake measurement[53,69].

2.2.2 ENERGY AND PROTEIN INTAKES IN PATIENTS WITH CANCER

As discussed, the information available in the literature regarding energy and nutrient intakes in patients with cancer is limited. That said, the collected data suggests that mean energy and nutrient intakes are inadequate to support weight maintenance and nutritional health in patients with advanced disease. Table 2.1 summarizes the dietary intake information collected for patients with various malignancies.

When compared to non-cancer age-matched controls, weight-losing cancer patients have shown a reduction in dietary energy intake of up to 40%[46,47] (Table 2.1). Mean dietary intakes reported by Levine and Morgan[47] are slightly lower than values described in the more substantial data sets discussed below, however, this is likely due to the fact that the studied population was in hospital at the time data was collected. Though limited by relatively small sample sizes, the results presented are similar to dietary intakes reported by the much larger studies described below.

Using multiple-day food records to collect dietary information, energy and protein intakes have been described in relatively large samples of patients with advanced cancer[10,36,37] (Table 2.1). Reported energy and protein intakes consistently show wide variation, ranging from 4 to 77kcal/kg BW/day and 0.2 to 3.1g/kg BW/day, respectively[10]. Across the three large-scale studies measuring baseline dietary intake prior to nutritional intervention and in the absence of anti-tumor treatment, mean energy intakes were similar and fell in the range of 1500 to 1700kcal/day, or approximately 26kcal/kg BW/day. Mean protein intakes, where reported, were in the range of 1g/kg BW/day; this corresponds to the lowest estimated requirement for this population. As previously discussed, the minimum estimated mean energy requirements for this population are likely to be upwards of 34kcal/kg BW/day. In all cases, the reported dietary intake values suggest that a large fraction of patients with advanced cancer are consuming amounts of dietary protein and energy that would be predicted to place them at risk of deficiency (Figure 2.1).

Table 2.1 Summary of baseline dietary information collected in individuals with advanced-stage malignancies

Study	n	Cancer Type	Mean Energy Intake ±SD kcal/d (kcal/kg/d)		Resting Energy Expenditure (kcal/kg/d)	Energy intake: Resting Energy Expenditure	Mean Protein Intake (± SD) g/d (g/kg/d)
			Cancer	Control			
Cohn et al[46]	6 Weight-losing Cancer vs 8 Healthy Controls	Various advanced-stage (III or IV) malignancies	1619	2448	Not measured	Not measured	75.2
Levine & Morgan[47]	10 Hospitalized Cancer vs 20 Hospitalized Controls	Various advanced-stage malignancies (stage not specified)	1428 ± 215 (24 ± 4)	2261 ± 120 (33 ± 4)	Not measured	Not measured	49 ± 8.0 (0.8 ± 0.1)
Bosaeus et al[10]	297 Cancer; no control	Mixed solid tumors	1716 ± 627 (26 ± 10)	N/A	23 ± 4	1.13	66 ± 24 (0.99 ± (0.39)
Lundholm et al[37]	309 Cancer; no control	Mixed solid tumors	1727 ± 55† (26*)	N/A	22.7 ± 0.3	1.14	Not measured
Fearon et al[36]	200 Cancer; no control	Pancreatic Cancer	1561 ± 53† (26*)	N/A	Not measured	Not measured	61.6 (1.01*)
Moses et al[16]	24 Cancer; no control	Pancreatic Cancer	1754 ± 95†	N/A	1387kcal/day	1.26*	54 ± 6

* value estimated using reported data (eg. Mean energy intake/mean body weight = estimated mean kcal/kg/day)

†Reported value mean ± standard error of the mean (SEM)

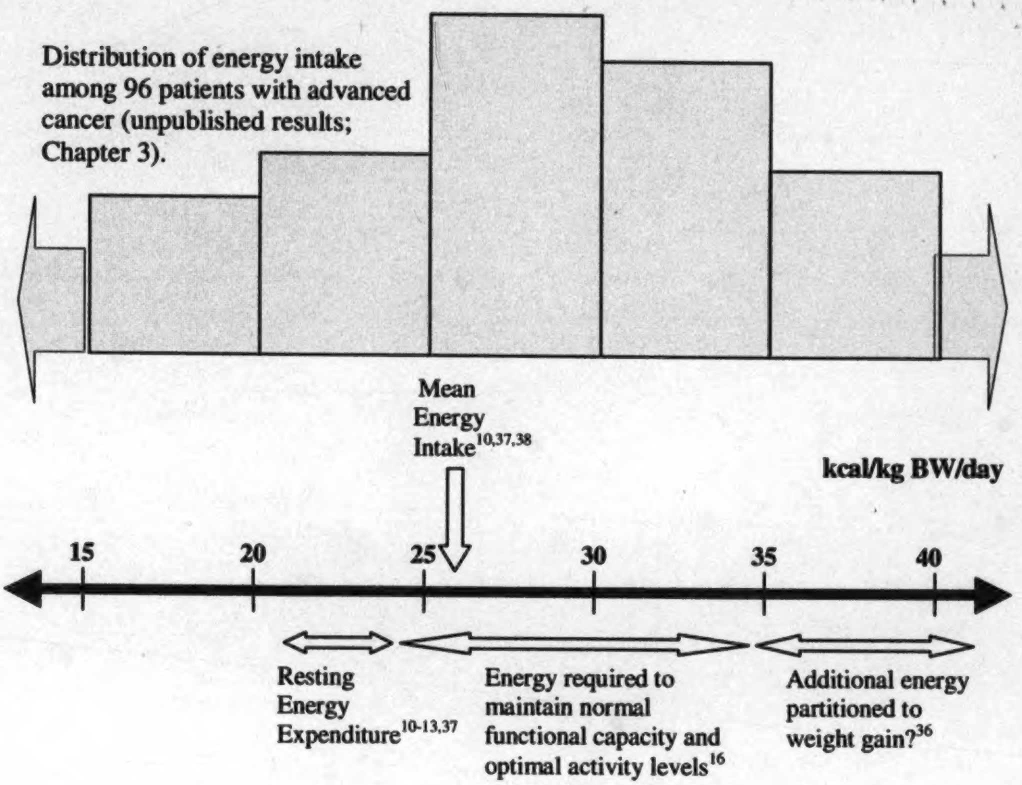
Distribution of energy intake among 96 patients with advanced cancer (unpublished results; Chapter 3).
Mean Energy Intake[10,37,38]
kcal/kg BW/day
15
20
25
30
35
40
Resting Energy Expenditure[10-13,37]
Energy required to maintain normal functional capacity and optimal activity levels[16]
Additional energy partitioned to weight gain?[36]

Figure 2.1. Estimated energy requirements and mean energy intake of patients with advanced cancer.

Micronutrient intakes are rarely reported among patients with cancer, and the little available information is limited to patients receiving therapy. While few, if any, studies have described micronutrient intakes among patients with advanced cancer, the decreased energy intakes that have been reported in this population are likely to result in corresponding micronutrient deficiencies. Further research relating to micronutrient requirements and describing intakes is required.

Though data is limited, it is widely accepted that energy intake is decreased in cancer patients relative to pre-diagnosis intake and age-matched controls[47-49]. Furthermore, the evidence suggests that for a large proportion of patients with advanced cancer, energy and protein intakes are below estimated requirements to maintain energy and nitrogen balance, and are therefore insufficient to support reversal of the wasting process and promote weight gain[16,36,37]. Related micronutrient deficiencies are likely. The heterogeneity of intakes is something that must be recognized and further explored in the literature. While the progressive wasting associated with advanced cancer is multifactorial, involving metabolic aberrations not found in simple starvation, the malnutrition resulting from hypophagia will exacerbate tissue losses. As such, numerous strategies to increase energy and protein intakes have been explored, including appetite stimulants, dietary supplementation and artificial nutrition support.

2.2.3 PHARMACOLOGICAL MANIPULATION OF APPETITE AND DIETARY SUPPLEMENTATION

As discussed, decreased appetite and interest in food are common problems in patients with advanced cancer. The pharmacological strategies to improve dietary intake have been reviewed recently and the reader is referred to MacDonald et al[2] for a full discussion of current clinical investigations in this area. At this time, two agents are prescribed in standard clinical practice: megestrol acetate and corticosteroids. Megestrol acetate is currently the gold standard treatment for improved appetite, but it has a limited efficacy and shows no benefit in up to 60 % of patients to which it is prescribed[70,71]. Corticosteroids tend to be beneficial only in the short-term[29].

Though some patients experience improved appetite with pharmacologic intervention, many still have difficulty meeting nutrient requirements and are encouraged to increase dietary intake using commercially available supplements. A benefit of liquid oral commercial supplements such as Boost® (Mead Johnson Nutritionals) and Ensure® (Abbott Laboratories) is that they are a convenient easy-to-consume nutrient-dense choice for patients who are having difficulty maintaining normal or adequate dietary intake. Though fish-oil enriched liquid oral supplements may increase dietary intake and improve physical activity and functional status[16,72], these are not yet widely available commercially. Furthermore, some studies have shown that supplements displace energy derived from traditional foods[36,73,74]; this may be of particular concern for patients experiencing early satiety, a common symptom in advanced cancer patients[27]. Though in certain cases commercial supplements may represent a nutrient dense dietary alternative, some patients may prefer traditional foods. In addition, flavor fatigue may become a problem for those regularly consuming this type of product. Nutrient augmentation of foods that are habitually consumed may be worthy of exploration.

2.3 FOOD CHOICE, FOOD PREFERENCES AND DIETARY PATTERN ANALYSIS

Eating serves more than a fundamental biological need and holds significance beyond providing essential nutrients; it is a source of enjoyment and comfort, and the foods we select can carry emotional meaning[75] and reflect self-image[76]. Therefore, food choice is a complex process influenced by hedonic preferences, cultural and social beliefs, health status, age, sex, and other demographic variables[77,78]. Given the complexity and individuality of food selection, it can be challenging to invoke dietary changes[78,79]. Recommendations that incorporate dietary habits and preferred foods are more likely to successfully evoke change than those which disregard typical dietary patterns and food preferences[79-82]. Previous research has shown that food acceptance by terminal cancer patients is improved when personal tastes and eating habits are considered[80,81].

A broad understanding of food preferences in this patient population would be a useful starting point for clinicians seeking to provide more individualized dietary recommendations. Patients with advanced cancer experience a myriad of symptoms that might be expected to affect food preferences and nutrient intakes, such as chemosensory alterations, pain, fatigue and depression[27]. Though anecdotal reports of specific food aversions are commonly referred to in the literature, very few studies have been conducted relating to food preferences among patients with cancer. Vickers et al[83] questioned 111 metastatic cancer patients and 205 healthy controls about their preference for various common food items and found that patients who reported the development of food aversions consistently rated red meats, poultry and chocolate as less pleasurable overall. DeWys and Walters[84] related specific food aversions and food choices to altered taste thresholds, a common symptom among patients with advanced cancer. The investigators found that patients with increased sensitivity to bitter taste were more likely to report an aversion to meat and other protein foods, while those complaining of general decline in taste sensitivity favored highly seasoned foods. A limitation of both studies is that patients were not asked to independently report preferred foods, but instead were provided with a list of food items and asked to rate their liking/disliking of only these foods. Such an approach would restrict the dietary information gathered to a relatively confined list of foods. Pettey et al[81] asked terminally ill patients to provide a list of currently favored foods upon admission to an oncology unit in order to develop a menu catering to food preferences. Among the 'favored foods' reported by the 25 participating individuals were hot cereals, soups, eggs, milkshakes, pudding, muffins, and cheese. Interestingly, hamburgers and hot dogs were also listed as satisfying and palatable among this patient group. While findings of this sort highlight the importance of individual counseling and tailored menus, the results do not provide a general characterization of food preference and dietary intake that can be considered representative of the advanced cancer population due to small patient numbers and methodological limitations.

Dietary pattern analysis can provide a broad picture of food selection and nutrient intake, characterizing the typical eating habits of a group of individuals. Dietary pattern analysis has been shown to be a useful approach to dietary assessment of a population[85-87], and has been used to investigate the relationship between complex dietary exposures and risk for disease. Dietary information collected using FFQs or dietary records can be classified into defined food categories depending on nutrient content and research goals. The patterns of food consumption are then derived from the food intake data using a multivariate statistical modeling technique such as factor analysis or cluster analysis. In factor analysis, the relationships among different food categories are assessed; foods are grouped together to define a dietary pattern based on the degree to which the foods are correlated with each other[85]. Khani et al[86] reported high reproducibility and validity of dietary patterns identified through factor analysis, supporting its use in nutritional epidemiology. However, the dietary patterns defined through factor analysis may be difficult to interpret because it is possible to classify individuals into more than one eating pattern. In contrast, cluster analysis aggregates people with similar food consumption patterns[85,88]. With this type of analysis, the diet patterns are non-overlapping such that individuals can be classified into one pattern only; clusters can subsequently be compared in terms of nutrient intake.

Numerous studies have shown cluster analysis to be a useful method for identifying different patterns of food consumption within a population, and for highlighting those foods and nutrients which are consumed in excessive or deficient amounts[87,89-95]. The validity of dietary patterns identified through cluster analysis was demonstrated by Quatramoni et al[87]; the clustering technique was shown to have high sensitivity and specificity for dietary factors. While the reproducibility of dietary patterns defined by cluster analysis has not been systematically assessed[85], it is supported by the fact that there is a reasonable consistency of reported dietary patterns among studies using cluster analysis to describe dietary behavior[82,90,91,93-95].

Nutrient intake is a function of the types and amount of foods chosen, therefore, different dietary habits and food intake patterns would be expected to confer varying levels of risk for malnutrition, obesity or chronic disease. Therefore, diet pattern analysis could provide the opportunity to assess both food preference and nutrient intakes in patients with advanced cancer, two largely-neglected areas of dietary research in this population. This would provide a solid foundation for the development of dietary recommendations for improved nutritional status.

2.4 CONCLUSION

Malnutrition is recognized as an indication of poor prognosis and a source of emotional distress among patients with advanced cancer. However, current dietary recommendations and nutrition interventions used in clinical practice for patients with advanced cancer are limited by a lack of basic dietary knowledge. A comprehensive understanding of nutrient requirements, current nutrient intakes and dietary preferences is essential in identifying limitations to nutritional health and in planning appropriate dietary interventions. Empirically determined disease- and stage-specific nutrient requirements have not been established and large scale investigations characterizing typical nutrient intakes and food consumption patterns are rare or absent from the literature. Steps must be taken to increase knowledge in this area with the aim to improve nutritional status in patients with advanced cancer.

In the absence of experimentally determined disease-specific nutrient requirements, nutrient intakes may be compared to DRIs established for healthy adults of comparable age, though these are likely to underestimate requirements in patients with advanced cancer. An understanding of which foods are consumed in excess or inadequate amounts within this population can help to identify nutrients for which intake may be insufficient, placing individuals at risk for deficiency. This can provide clinicians with a basis on which to plan nutrition intervention strategies and supplementation trials for optimized nutrient intakes and improved nutritional status. Dietary pattern analysis may be an appropriate tool to characterize typical eating patterns and food preferences.

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CHAPTER THREE

3.0 DIETARY PATTERNS IN PATIENTS WITH ADVANCED CANCER: IMPLICATIONS FOR ANOREXIA-CACHEXIA THERAPY

3.1 INTRODUCTION

Many patients with advanced cancer suffer from cachexia[1], a wasting syndrome characterized by anorexia, asthenia, and profound losses of adipose tissue and skeletal muscle mass. The association of anorexia-cachexia syndrome with poor prognosis, loss of functional status and poor quality of life has motivated researchers to develop therapeutic strategies for this problem. The scope of current understanding of the biochemical mechanisms of cancer cachexia and the current and investigational therapeutic approaches were reviewed recently[2]. Some of these interventions are directed at the attenuation of catabolic processes and hypermetabolism. Another major category of anorexia-cachexia therapy is based upon the concept that cancer cachexia is, at least in part, a form of malnutrition. Orexigenic agents, including glucocorticoids[3], the progestational agents[3-11] and dronabinol[7,11], are intended to promote voluntary food intake. Supplementation with specific foods or nutrients that may be deficient such as amino acids and n-3 polyunsaturated fatty acids is also a current theme[12-17].

An understanding of the food preferences, dietary habits, nutrient intakes and dietary requirements of a population is essential for the development of recommendations to maintain or improve health or quality of life[18]. Surprisingly, the clinical studies of pharmacologic intervention and nutrient supplementation targeting anorexia and wasting in patients with advanced cancer are not framed within the context of current intake or food preferences; in fact, the typical nutrient intakes and food choices for individuals with advanced cancer are not well documented. The dietary information reported for patients with cancer may be of limited applicability because of small patient numbers and subsets of disease types and stages that may not be representative of the population. Some studies focus very specifically on nutritional impact of chemotherapy, radiation or surgery. In many studies it is frequently unclear as to when during the disease trajectory data was collected.

It is standard dietetic practice to consider a patient's current dietary habits, requirements and preferences when providing dietary recommendations. Previous research has shown that food acceptance by cancer patients is improved when personal tastes and eating habits are considered[19,20]. In a recent search of the literature, we could find no citation regarding dietary patterns in patient populations with advanced cancer. This would appear to be an important deficit in current understanding. In order to identify specific nutrients that are at risk for deficiency, and to best determine levels at which nutrient supplementation may provide added benefit, current nutrient intakes must first be known. None of the strategies for management of cachexia are likely to be entirely effective unless coupled with adequate intakes of all classes of essential nutrients.

Dietary pattern analysis can provide a broad picture of food and nutrient intake, characterizing the typical eating habits of a group of individuals[21,22]. Numerous studies have shown cluster analysis to be a useful method for identifying different patterns of food consumption within a population[21-30]. Therefore, the objectives of this study were to (a) describe food and nutrient intakes and identify dietary patterns in a population of patients with advanced cancer similar to patient populations reported in clinical trials of anorexia-cachexia therapy, (b) explore the relationship between dietary pattern and nutrient intake, and (c) examine the relationship between dietary pattern, weight loss and patient survival.

3.2 PATIENTS AND METHODS

3.2.1 STUDY POPULATION AND DATA COLLECTION

Subjects with advanced cancer (defined as locally recurrent or metastatic, n=96) were recruited either from the metastatic clinics of the Cross Cancer Institute, a cancer treatment center serving Edmonton and northern Alberta, or from the Palliative Home Care program serving Edmonton. None of the patients were currently receiving radiation or chemotherapy. The studies were reviewed and approved by the Alberta Cancer Board Research Ethics Board and the Health Research Ethics Board of the University of Alberta. All participants spoke English and provided written informed consent. All subjects were resident in their homes and were assumed to make food choices by personal preference. Institutionalized patients were excluded.

Dietary records (detailing intake for 3 consecutive days, including 1 weekend day and 2 weekdays) were used to assess subjects' nutrient intakes and meal patterns, a method that has been shown to adequately reflect current dietary intake [31,32] and provide mean estimates of group dietary intake[33]. The record consisted of 6 fields to be completed each day, corresponding to three main meals (breakfast, lunch, supper) and three between–meal snacks (morning, afternoon, evening). A research assistant familiar with cancer patients in palliative care and skilled in the administration of diverse data collection tools, instructed participants on completion of the food record. Food records were reviewed with the study participant for accuracy and completeness. Meals or snacks not taken were annotated by the patient "no food / or beverage taken".

Each subject's height and weight were measured, and in any case where a participant was bedridden or unable to stand unsupported, the most recently recorded values were taken from the patient's medical chart. Body mass index (BMI, kg/m^2) was calculated from these values. Information regarding history of weight loss, defined in this case as weight loss within the previous 6 months, was self-reported. Date of death was confirmed from institutional records.

Concurrent symptom burden (pain, appetite, tiredness and sadness) was assessed using the use of the Edmonton Symptom Assessment Scale (ESAS)[34] or Functional Assessment of Anorexia-Cachexia Therapy Version 4© (Copyright David Cella, Phd) (FAACT)[35].

3.2.2 DATA ANALYSES

Nutrient intakes were estimated using the Canadian Nutrient File Database of the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR). Analysis focused on energy and protein intake, percent total energy contributions (% kcal) from fat, carbohydrate, and protein, as well as selected micronutrients, including vitamin C, calcium and iron. Mean energy and protein intakes were expressed per person/day and per kg body weight (BW)/day.

Dietary pattern analysis has been shown to be a useful and valid approach to dietary assessment of a population[21-30], however there are several limitations. Cluster analysis is an empirical statistical method and as such is data-driven; essentially, the selection of the final cluster solution has a subjective component. Care must be taken to identify the solution showing good cluster separation (see below). Despite these limitations, there appears to be reasonable consistency among studies describing dietary patterns[18,23-26,30].

For the dietary pattern analysis, food items were classified into one of 20 food categories based on similarities or differences in macronutrient composition and culinary role[23-25] (Table 3.1). The food selection data was standardized by % energy contribution to total energy intake[23,25]. Because cluster analysis is sensitive to outliers, extreme values were 'winsorized'[24]; that is, average energy contribution values for any food category that were ≥5 times the standard deviation (SD) from the mean were assigned the next lowest value of energy contribution for that food category. This procedure was carried out in less than 0.5% of all data points. In addition to the cluster analysis, individuals categorized as having abnormal eating behaviors were further characterized using descriptive statistics. Eating behavior was considered abnormal if (a) >50% of energy was derived from one food category, and/or (b) the average energy contribution for one or more food categories was >35% and ≥5 SD from the population mean.

Table 3.1 Definition of food categories used in cluster analysis

Food Categories	Items
Butter/margarine/fats	Butter, margarine, oils
Beans	Beans, dry peas, baked beans and pork, cowpeas, soybeans, tofu, meat substitutes made from soy products, and soymilk
Cereals	Highly fortified cereal, cooked cereal, other cold cereals
Cheese	Cheeses and cheese spread
Dark Bread	Dark bread, including whole wheat, rye and pumpernickel
Desserts	Doughnuts, cookies, cakes, pastries, pie
Egg	Eggs (all preparations)
Fruit	All fruits and juices including citrus fruits and juices
Ice cream	Ice creams
Milk	Skim, 1%, 2% or whole milk; beverages made with milk
Nut	Nuts and nut butters
Pasta	White rice, mixed dishes with rice, rice and beans, pastas, dishes made with pastas
Potato	Baked, boiled, mashed potatoes, potatoes all preparations including fried potato (hashbrowns, french fries)
Meats	Beef roast, steak, beef stews, ground beef, mixed dishes with meat; chicken, turkey (all preparations); Processed lunch meats, sausage, hot dogs, bacon; fish, fresh, frozen or canned; seafood
Salty Snack	Salty snacks such as chips, popcorn
Soups	All soups
Supplement	Ensure®, Boost®, Carnation Instant Breakfast®, and other meal-replacement products
Vegetable	Tomatoes, tomato juice, onions, celery, lettuce, salad, radishes, green beans, green/red peppers, broccoli, spinach, carrots, yams, etc
White Bread	White bread including rolls, buns, crackers, bagels, pancakes, waffles
Other	Condiments (such as ketchup or mustard), alcoholic beverages, drink crystals, pops or sodas, hard candies

The chosen cluster solution was validated in the following manner to ensure that the resulting dietary patterns were representative of the population: the cluster analysis was run on (a) the entire data set with a range of predefined cluster numbers, (b) randomly selected proportions of the data set, and (c) subsets of the data set classified by gender[24]. Consequently, the food groups that consistently defined and separated the clusters were identified. Once the 3 cluster solution was validated, one-factor analysis of variance (with PDIFF option for pairwise t-tests and contrast option for customized hypothesis tests) was used to compare the mean energy contribution from each food category, energy and nutrient intakes for selected macro- and micronutrients, and continuous clinical variables across the 3 clusters. Differences in nutrient intakes and weight loss across clusters were tested controlling for total energy intake. χ^2 analysis was used to test proportional differences among clusters (gender, prevalence of weight loss). All statistical analyses were performed using the Statistical Analysis System (SAS for Windows, version 8.2., 1999, SAS Institute Inc, Cary NC).

3.3 RESULTS

Characteristics of the study population are shown in Table 3.2. Because preliminary analyses showed similar diet patterns and nutrient intakes between males and females, further analyses were not classified by gender. Dietary information was recorded, on average, at 7.5 months prior to death (range 0.5 -24 months).

Table 3.2 Characteristics of study population

Characteristics	Females	Males	Total
Number of subjects [*n* (%)]	41 (42.7)	55 (57.3)	96 (100)
Age (y)	60.0 ± 11.1[1]	65.2 ± 9.2	63.0 ± 10.4
BMI (kg/m^2)	22.1 ± 4.9	23.1 ± 4.1	22.7 ± 4.5
Weight loss (kg)[2,3]	10.5 ± 10.8	13.4 ± 8.6	12.2 ± 9.6
Weight loss (%)[2,3]	14.1 ± 13.3	15.9 ± 10.2	15.1 ± 11.5
Time to death (months)	7.9 ± 7.8	7.3 ± 6.9	7.5 ± 7.2
Primary site of tumor [*n* (%)]			
Lung	11 (11.4)	10 (10.4)	21 (21.9)
Gastrointestinal	7 (7.3)	22 (22.9)	29 (30.2)
Breast	15 (15.6)	0 (0)	15 (15.6)
Prostate	0 (0)	11 (11.4)	11 (11.4)
Other	8 (8.3)	12 (12.5)	20 (20.8)

[1] *mean* ± SD.
[2] Adjusted for energy intake
[3] Weight lost over previous 6 months

Abbreviations: BMI, body mass index; SD, standard deviation.

Energy and nutrient intakes showed a striking degree of variability (Table 3.3). Energy intake was determined to be normally distributed based on the skew and kurtosis of the distribution, which were not significantly different from a normal distribution ($P >$ 0.05). The study population had a mean energy intake of 1578 ± 699 kcal/day (mean ± standard deviation) (range 290 to 3926 kcal/day) or 25 ± 10 kcal/kg BW/day (range 4 to 51kcal/kg BW/day) (Table 3.3; Figure 3.1). Eighty-two percent (n=79) of the participants had an energy intake below 34 kcal/kg BW/day. Mean protein intake was 63 ± 27g/day (range 6 to 169g/day) or 1.0 ± 0.4g/kg BW/day (range 0.1 to 2.4g/kg BW/day). When patients were stratified according to energy intake (kcal/kg BW/day), no significant differences in survival or % weight loss were observed.

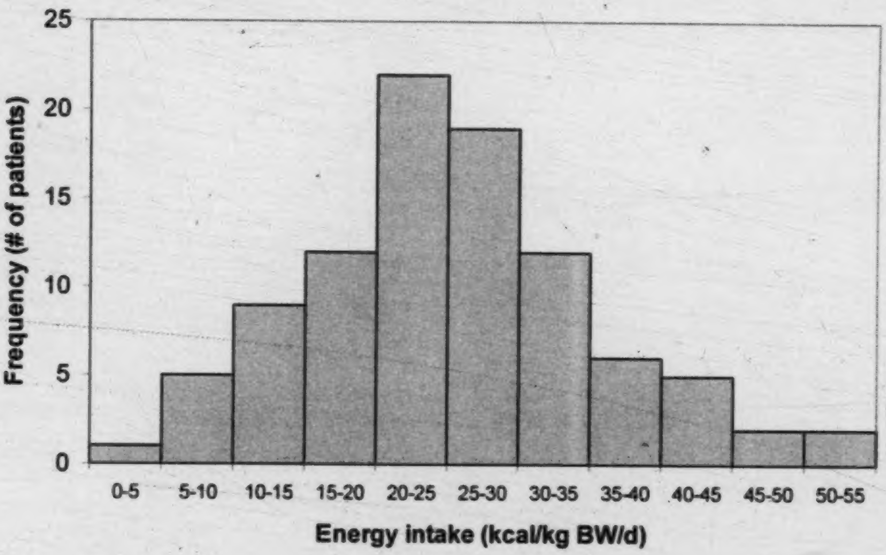

Figure 3.1. Distribution of energy intakes of the study population (kcal/kg BW/day)

The average energy contributions from the 20 food categories are shown in Table 3.4 and are diagrammed in Appendix A. For the population as a whole, meats provided the highest proportion of energy relative to all other food categories (14.1 ± 9.6%, $P < .0001$). Additional foods providing a significant percentage of total calories included dessert (9.8 ± 8.4%), fruit (8.5 ± 8.2%), white bread (8.5 ± 8.9%), and milk (8.1 ± 8.4%). The supplement food category, consisting mostly of products such as Ensure® (Abbott Laboratories) or Boost® (Mead Johnson Nutritionals), provided an average of 6.0 ± 11.8% of energy, ranging from 0 to 57% of total calories. Among those individuals taking commercial supplements (n=30 of 96 subjects), this food category provided an average of 19.1 ± 14.0% of total energy consumed.

Table 3.3 Energy and nutrient intakes for the total study population and by dietary pattern

	Population Totals		Milk and Soup 'Liquid'		Fruit and White Bread		"Traditional" Meat and Potato			
	n= 96		*n*=36		*n*= 14		*n*=46			
Nutrient	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	*p*-value[1]	PDIFF
Total energy										
Absolute (kcal/day)	1578 (1484)	699	1554 (1397)	839	1200 (1222)	525	1713(1655)	584	0.0521 (NS)	-
kcal/kg BW/day	25.3 (24.4)	10.0	24.3 (23.2)	10.9	19.9 (19.7)	8.2	27.7 (26.3)	9.2	0.0293	3>2
Protein										
Absolute (g/day)	63 (64)	28	61 (50)	34	50 (49)	26	69 (67)	21	0.0539 (NS)	-
g/kg BW/day	1.0 (1.0)	0.4	1.0 (0.9)	0.5	0.8 (0.9)	0.4	1.1 (1.1)	0.3	0.0290	3>2
g/kg BW/day[2]	1.0 (1.0)	0.4	1.0 (0.9)	0.5	1.0 (0.9)	0.4	1.0 (1.1)	0.3	0.7216 (NS)	-
Energy by macronutrient										
Carbohydrate (% kcal)	54.7 (54.0)	7.3	55.9 (56.2)	4.9	60.8 (56.7)	12.6	51.8 (51.6)	5.3	<0.0001	2>1>3
Fat (% kcal)	30.6 (31.7)	6.1	29.6 (29.6)	5.2	26.0 (28.1)	9.6	32.8 (32.5)	4.5	0.0004	3>1>2
Protein (%kcal)	15.9 (15.8)	3.8	15.6 (15.7)	3.9	14.4 (15.7)	3.8	16.6 (15.8)	3.5	0.1473 (NS)	-
Micronutrients										
Calcium (mg/day)	780 (645)	500	955 (820)	629	589 (366)	493	701 (604)	327	0.0205	1>2,3
Calcium (mg/1000kcal/day)	516 (464)	305	635 (597)	208	535 (326)	640	417 (393)	153	0.0045	1>3
Iron (mg/day)	14.2 (13.1)	7.1	15.7 (13.9)	8.4	10.4 (11.3)	5.2	14.3 (13.2)	6.1	0.0594 (NS)	-
Iron (mg/1000kcal/day)	9.3 (8.3)	3.6	10.6 (10.4)	3.4	9.1 (7.0)	5.6	8.4 (7.6)	2.5	0.0197	1>3
Vitamin C (mg/day)	129 (95)	133	107 (92)	64	129 (93)	91	147 (99)	177	0.4109 (NS)	-
Vitamin C (mg/1000kcal/day)	87 (65)	89	[illegible]	34	141 (76)	142	83 (56)	94	0.0395	2>1,3

[1] NOTE: The P-values reported in the table refer to the results of the Analysis of Variance

[2] Adjusted for energy intake

Abbreviations: SD, standard deviation; kcal, kilocalories; BW, body weight; NS, not significant at α=0.05.

Table 3.4 Percentage energy contributions from food categories for the total study population and the 3 dietary intake patterns (%kcal/day)

Food or food category	**Population Totals** *n*=96		Milk and Soup 'Liquid' *n*= 36		Fruit and White Bread *n* = 14		"Traditional" Meat and Potato *n* = 46		*p*-value[1]	PDIFF
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Butter/margarine/fats	1.7	2.1	0.6	1.2	0.7	0.9	2.8	2.3	<0.0001	3 > 1,2
Beans	0.9	2.1	0.2	1.0	0.0	0.0	1.7	2.8	0.0023	3 > 1,2
Cereals	6.2	6.5	10.1	6.4	1.7	2.8	4.5	5.7	<0.0001	1 > 2,3
Cheese	2.0	2.8	1.5	2.0	1.9	3.1	2.5	3.2	NS	-
Dark Bread	3.6	4.8	4.0	4.5	0.8	2.7	4.2	5.3	NS	-
Desserts	9.8	8.4	11.4	9.4	4.3	6.1	10.2	7.7	0.0231	1,3 > 2
Egg	3.1	3.7	1.7	2.5	3.5	4.2	4.0	4.0	0.0141	3 > 1
Fruit	8.5	8.2	7.9	6.1	15.3	14.8	6.9	6.3	0.0033	2 > 1,3
Ice cream	1.8	3.5	2.1	4.4	0.9	1.9	1.8	2.9	NS	-
Milk	8.1	8.4	14.1	10.1	3.6	6.1	4.8	3.8	<0.0001	1 > 2,3
Nut	1.4	3.1	1.4	3.5	1.4	2.5	1.4	2.9	NS	-
Pasta	6.1	6.7	5.4	6.0	10.1	8.9	5.5	6.8	NS	-
Potato	4.0	4.3	1.8	2.9	2.4	2.5	6.2	4.6	<0.0001	3 > 1,2
Meat	14.1	9.6	9.7	8.0	11.1	9.9	18.4	9.1	<0.0001	3 > 1,2
Salty snack	0.7	1.6	0.1	0.8	0.6	1.7	1.1	2.1	NS	-
Soups	4.8	5.7	7.9	8.1	3.8	4.8	2.6	3.0	0.0003	1 > 2,3
Supplement	6.0	11.8	8.2	14.2	11.8	15.6	2.5	6.4	0.0123	1,2 > 3
Vegetable	2.0	2.2	1.2	1.5	1.1	1.4	2.9	2.5	0.0007	3 > 1,2
White bread	8.5	8.9	5.7	6.9	15.4	15.2	8.6	8.1	0.0046	2 > 1,3
Other	4.5	5.9	2.9	3.7	6.3	10.1	5.2	5.4	NS	-

[1] NOTE: The P-values reported in the table refer to the results of the Analysis of Variance

Abbreviations: SD, standard deviation; NS, not significant at α =0.05.

3.3.1 DIETARY PATTERNS IDENTIFIED BY CLUSTER ANALYSIS

The validation testing of the 3 cluster solution consistently identified milk, meat, and fruit as the food categories providing the greatest division among clusters (Table 3.4, Appendix A). The "Milk and Soup Liquid" pattern (n = 36) had a 3-4-fold higher energy contribution from milk than the other clusters ($P < .0001$), despite the frequent usage of fat-reduced milk products by individuals in this group (Table 3.4). Only 14% (n=6) of individuals in this group chose whole milk or cream over available fat-reduced dairy products. This diet pattern also had the highest average energy contributions from soup and cereals (largely hot cereals). Individuals in this category also had high energy contributions from desserts and a mean energy contribution of 8.2 ± 14.2% from commercial supplements.

The "Fruit and White Bread" (n = 14) pattern showed the highest mean energy contribution from fruit (largely from fruit juice) and white bread. This dietary pattern was also notable for having the highest energy contribution from commercial supplements (11.8 ± 15.6%) and the lowest energy contribution from desserts (4.3 ± 6.1%) relative to the other intake patterns. An important feature of this pattern is that a high proportion of the total caloric intake was contributed by the least variety of foods; over 40% of calories were provided by the fruit, white bread and supplement food categories.

The "Traditional Meat and Potato" pattern (n = 46), had a significantly higher intake of these food categories as well as the 'butter, margarine and added fats' category. This diet pattern had the lowest average energy contribution from commercial supplements (2.5 ± 6.4%, $P = .0031$). While the meat category provided a large fraction of total energy (18.4 ± 9.1%), this dietary pattern showed the widest variety of food energy sources overall.

3.3.2 NUTRIENT INTAKES BY CLUSTER

Significant differences in mean energy and nutrient intakes were evident across dietary intake patterns (Table 3.3). The "Fruit and White Bread" pattern had lower energy and protein intakes relative to the "Traditional Meat and Potato" pattern (ie 19.9 ± 8.2 kcal/kg BW/day vs. 27.7 ± 9.2 kcal/kg BW/day, *P* = .0107). After adjusting for energy intake, it is clear that the dissimilarities in protein intake among clusters are associated with caloric intake (*P* < .0001), which itself is a function of dietary pattern. Mean absolute energy (kcal/day) and protein (g/day) intakes showed a trend towards similar differences between clusters (*P* = .0521 and *P* = .0539, respectively).

Percentage of energy from fat (*P* = .0004) and carbohydrate (*P* < .0001) were different among dietary patterns; however, there was no difference among patterns for the percentage of energy from protein (*P* = .1473). The "Traditional" dietary pattern had the highest mean % of energy from fat (32.8 ± 4.5%) and the lowest mean % of energy from carbohydrate (51.8 ± 5.3%). The opposite dietary macronutrient composition was observed in the "Fruit and White Bread" pattern, which had the lowest mean % energy contribution from fat (26.0 ± 9.6 %) and the highest mean % energy contribution from carbohydrate (60.8 ± 12.6%). Individuals in the "Milk and Soup Liquid" diet pattern had the highest calcium intake (955 ± 629 mg/day, *P* = .0015) and the highest energy-adjusted intakes for calcium and iron. The "Fruit and White Bread" pattern had the lowest average intakes of all investigated micronutrients except vitamin C, findings that correspond with the high energy contribution from fruit and low overall energy and protein intakes reported for this dietary pattern.

3.3.3 CLINICAL VARIABLES BY CLUSTER

Weight and survival information for the diet patterns are shown in Table 3.5. A smaller proportion of individuals in the "Meat and Potato Traditional" pattern had experienced any amount of weight loss in the previous 6 months, relative to the other dietary patterns (χ=5.94, *P* =.0148). After adjusting for diagnosis, and energy (kcal/kg BW/day) and protein (g/kg BW/day) intakes, individuals with the "Milk and Soup Liquid" dietary pattern had a greater absolute weight loss (15.9 ± 11.3kg) relative to both the "Fruit and White Bread"(10.0 ± 4.4kg, *P* = .0492) and "Traditional" diet patterns (9.8 ± 8.6kg, *P* = .0101). The "Milk and Soup Liquid" pattern also had a greater percent weight loss compared to the "Traditional" pattern (19.6 ± 12.2 % vs. 11.6 ± 11.4%, *P* = .0030). BMI and time to death were similar across clusters (*P* = .6141 and *P* = .2912, respectively).

Table 3.5 Clinical Variables by Dietary Intake Pattern

	Milk and Soup 'Liquid' *n*=36		Fruit and White Bread *n*=14		"Traditional" Meat and Potato *n*=46			
Clinical Variable	Mean	SD	Mean	SD	Mean	SD	*p*-value[1]	PDIFF
BMI (kg/m^2)	**23.0**	**4.7**	**21.6**	**3.9**	**22.8**	**4.5**	**0.6141 (NS)**	**-**
Acute weight loss								
absolute (kg)^{2,3}	**15.9**	**11.3**	**10.0**	**4.4**	**9.8**	**8.6**	**0.0125**	**1>2,3**
% weight loss (%)^{2,3}	**19.6**	**12.2**	**14.8**	**6.8**	**11.6**	**11.4**	**0.0118**	**1>3**
Time to death (months)^2	**5.9**	**6.0**	**8.7**	**8.5**	**8.8**	**7.7**	**0.2912 (NS)**	**-**

[1] NOTE: The P-values reported in the table refer to the results of the Analysis of Variance

[2] Adjusted for energy (g/kg BW/day) and protein (g/kg BW/day) intake and diagnosis

[3] Weight loss over previous 6 months

Abbreviations: SD, standard deviation; BMI, body mass index; NS, not significant at $\alpha=0.05$; BW, body weight.

3.3.4 ABNORMAL EATING BEHAVIOR

Several individuals (n = 6) exhibited unusual or aberrant eating behavior. For example, one subject's diet was comprised almost entirely of fruit juice, which provided approximately 80% of total caloric intake. For two individuals, commercial supplements contributed over 50% of total energy intake. Homemade supplements prepared with ice cream provided over 40% of calories for one subject. For another, soup provided the greatest sustenance, contributing almost 40% of total energy. One individual consumed over 50% of total calories from homemade bread. One subject reported adherence to a macrobiotic diet, a restrictive diet that severely limited food choice. The mean energy and protein intakes for individuals demonstrating these behaviors (n=6) were 18.7 ± 6.9kcal/kg BW/day and 0.7 ± 0.4g/kg BW/day, respectively.

3.3.5 MEAL PATTERN ANALYSIS

Caloric content of individual meals and snacks were determined and the frequency of eating episodes was assessed. The total number of meals and between-meal episodes of eating ranged from 6 per 3 days to the maximum permitted on the food record (18 per 3 days). When the frequency of eating was divided into 3 groups (6-9; 10-14; 15-18 meals or snacks per 3 days), there was a significant relationship with total caloric intake, with the lowest frequency of food consumption associating with the lowest overall energy intakes (Figure 3.2, Table 3.6). There was a very low incidence of missed meals, such that 95-97% of all subjects reported consumption of breakfast, lunch and supper on all 3 study days. Though there were observed differences among groups in the caloric content of lunch and supper, the greatest differences were seen with caloric content of snacks (Figure 3.2, Table 3.6). Thus the variation in total energy intake and of eating frequency was largely accounted for by the variation in food consumption between meals (Table 3.6). The total caloric intake from meals on average was moderate being 384 kcal at breakfast; 447 kcal at lunch; 588 kcal at the evening meal. A small fraction of patients reported intakes higher than 1000 kcal at breakfast (2.7%) or lunch (3.1%) and 11.3% of patients consumed over 1000 kcal at the evening meal. Clinical variables by frequency of eating are shown in Table 3.7.

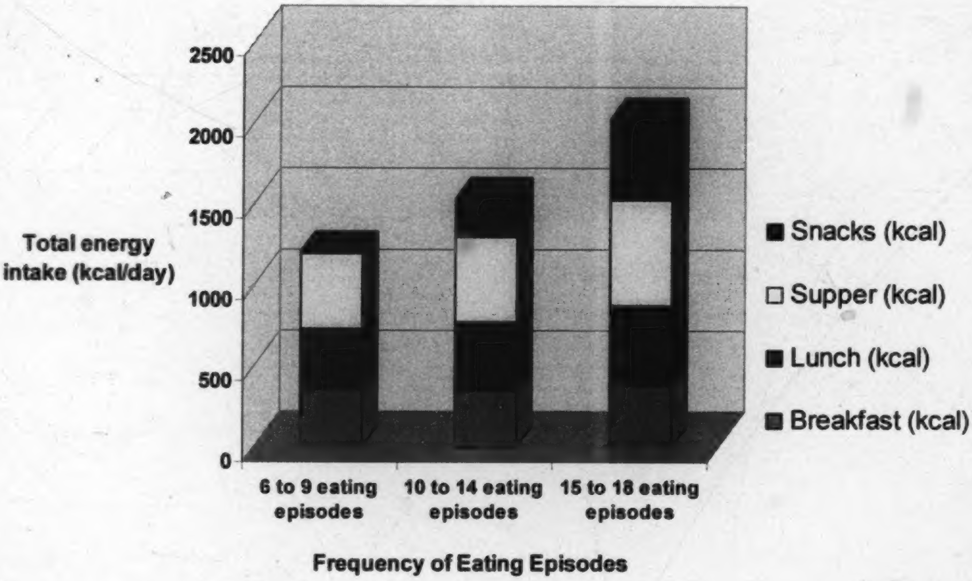

Figure 3.2 Caloric intake (kcal/day) by meal and frequency of eating episodes over 3 days

Table 3.6 Caloric intake (kcal/d) by meal and frequency of eating episodes over 3 days

	6 - 9 Eating Episodes		10 - 14 Eating Episodes		15 - 18 Eating Episodes			
	n = 26		n = 45		n = 22			
	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	*p*-value[1]	PDIFF
Breakfast (kcal/day)	355 (306)	270	350 (310)	242	381 (332)	220	0.6871 (NS)	-
Lunch (kcal/day)	377 (365)	246	416 (397)	246	494 (441)	309	0.0276	3 > 1
Supper (kcal/day)	462 (434)	282	527 (551)	302	649 (627)	345	0.0014	3 > 1,2
Snacks (kcal/day)	14 (0)	62	237 (203)	247	498 (452)	357	<0.0001	3 > 2 > 1
Total Daily Intake (kcal/day)	1209 (1176)	533	1538 (1558)	656	2044 (1900)	855	<0.0001	3 > 2 > 1

[1] NOTE: The P-values reported in the table refer to the results of the Analysis of Variance

Abbreviations: kcal, kilocalories; SD, standard deviation; NS, not significant at $\alpha = 0.05$.

Table 3.7 Clinical variables by frequency of eating episodes over 3 days

	6-9 Eating Episodes n = 26		10-14 Eating Episodes n = 45		15-18 Eating Episodes n = 22			
	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	*p*-value[1]	PDIFF
Age (y)	66 (63)	11.5	61 (61)	9.9	65 (66)	11.3		-
Absolute Weight (kg)	60.8 (58.6)	13.6	63.4 (61.5)	15.0	69.9 (70.5)	15.9	0.0994 (NS)	-
% Weight Loss[2]	18.5 (16.5)	10.1	15.1 (13.7)	11.2	10.0 (9.0)	8.8	0.0218	1 > 3
BMI	21.4 (20.3)	4.0	23.0 (22.4)	5.3	24.3 (24.1)	3.7	0.0831 (NS)	-
Months to Death	7.90 (6.0)	7.00	7.70 (5.70)	6.80	3.90 (2.6)	3.40	0.1002 (NS)	-
Total Daily Intake								
kcal/day	1209 (1176)	533	1538 (1558)	656	2044 (1900)	855	<0.0001	3 > 2 > 1
kcal/kg BW/day	20.5 (19.0)	7.6	26.4 (25.8)	10.5	32.8 (28.7)	13.0	0.0003	3 > 1,2

[1] NOTE: The P-values reported in the table refer to the results of the Analysis of Variance

[2] Weight loss over previous 6 months

Abbreviations: SD, standard deviation; y, year; BMI, body mass index; kcal, kilocalories; BW, body weight; NS, not significant at α=0.05.

The wide range of energy intakes as well as the number of eating episodes per day appeared to be unrelated to proximity to death (Figure 3.3A and Figure 3.3B). It is not possible with presently available data to explain this feature. Preliminary analysis revealed no relationship between energy intake (kcal/kg BW/day) and patient-generated scores for pain, appetite, or tiredness, however caloric intake was inversely related to patient scores for 'sadness' (data not shown). The relationship between self-perceived chemosensory abnormalities and energy intake is assessed in Chapter Five.

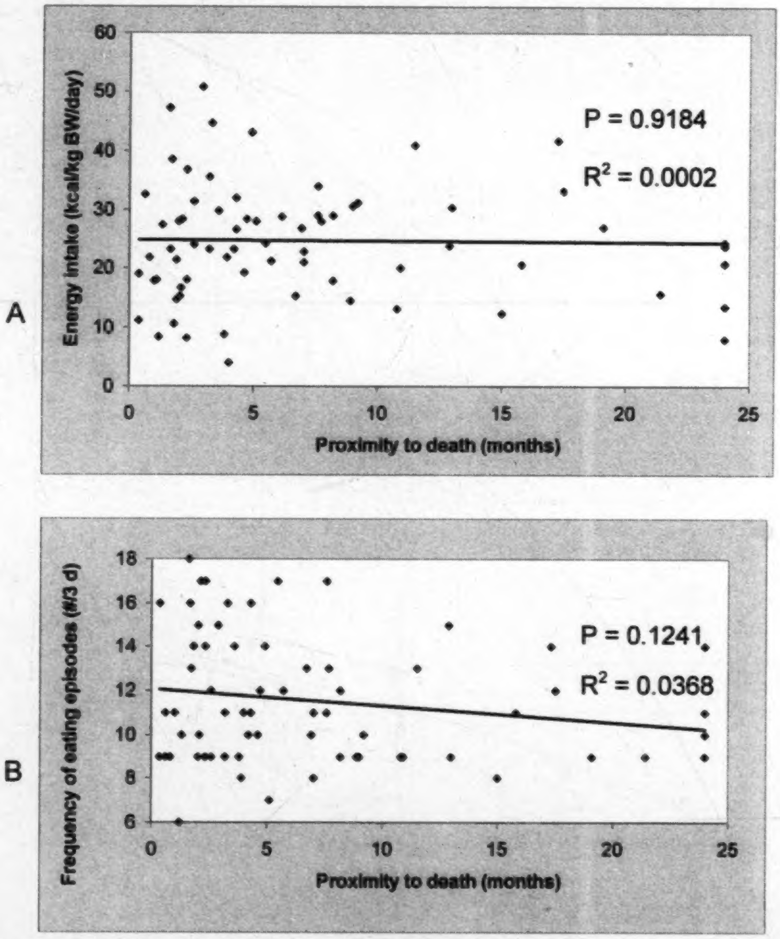

Figure 3.3 (A) Energy intake in relation to proximity to death, (B) Frequency of eating in relation to proximity to death.

3.4 DISCUSSION

3.4.1 METHODOLOGICAL CONSIDERATIONS

Typical food and nutrient intakes among a group of individuals with advanced cancer were characterized. The following methodological issues influence the interpretation of our data. The accuracy of self-reported food records has been drawn into question by reports that obese subjects tend to overestimate or underestimate the intake of certain foods[37-39]. It remains to be determined how accurately cancer patients affected by wasting syndromes report dietary records, although Bruera et al.[31] found good correspondence between 24-hour food records and actual energy and protein intake. Cognitive impairment or pressing symptomatic concerns (ie pain) may potentially influence the accuracy of food records. While the collection of records for an extended time may provide a better estimate of usual intake in the healthy population, the high subject burden and extended time period make this method unsuitable for patients with advanced cancer. Three days of data collection was selected here as a compromise between the extensiveness of the record and the relative frailty and vulnerability of the patients.

3.4.2 LOW ENERGY AND PROTEIN INTAKES WITH A WIDE DEGREE OF VARIATION

Patients in our study population consumed daily main meals, and with varying frequency, between-meal snacks. The frequency of food consumption that patients were given the opportunity to report (0-18 meals or snacks over 3 dayd) showed a positive relationship with total caloric intake, and this relationship was largely derived from the consumption of food outside of the 3 main meals of the day. All bouts of food consumption were of relatively modest proportions and this may be related to factors such as delayed gastric emptying, hypo-motility of the gut and early satiety[53]. Since capacity for intake at any given meal appeared to be limited, the frequency of eating emerged as an important variable in total energy intake. Such results support the use of high nutritional value snacks for improvement of protein and energy intakes.

An important feature of the population is the heterogeneity in terms of nutrient intake and food choice. Energy intake was normally distributed but showed wide variation (4.0- 51.2 kcal/kg BW/day). Much of this range is likely to be insufficient, however there is an important lack of objectively in determining nutrient requirements in advanced cancer patients, and while it may be difficult to know what the requirements are, there are several standards by which we can compare the nutrient intakes. The average resting energy expenditure (REE) of a population of advanced cancer patients with comparable age and diagnosis has been measured to fall between 22.0kcal/kg BW/day and 23.6 kcal/kg BW/day, and by this benchmark a 45% of our patients had energy intakes insufficient to support basal metabolism[40-42]. A stress factor of 1.2 to 1.5 times the REE is currently recommended in clinical practice for weight maintenance in cancer patients[43-44], which would equate to a minimum estimated average energy requirement of 26.4 – 34.0 kcal/kg/day to achieve weight maintenance; more than half of our patients reported intakes below the minimum estimated value. Lundholm et al[45] recently reported evidence suggesting that requirements for weight maintenance fall towards the upper level of this range at 34kcal/kg BW/day. By this estimation, over 80% of the subjects in our study had estimated energy intakes below requirement for weight maintenance. The standard protein intake recommended for weight maintenance in patients with cancer, depending on treatment regimen and nutritional status, is between

1.0 to 2.0g protein/kg BW/day[43]. A large proportion of individuals in our sample did not meet these recommendations, with 47% of participants reporting a mean protein intake below 1.0g protein/ kg BW/day.

3.4.3 THREE DISTINCTIVE DIETARY PATTERNS

Three dietary patterns emerged through cluster analysis. Numerous individuals followed a "Traditional" dietary pattern that emphasized meat and potato, had a higher fat content and a relatively even distribution of energy across food categories. Similar diet patterns have consistently been identified in healthy populations with similar age and gender distributions[24-26,30,48]. This may reflect the capacity of some individuals to enjoy traditional foods and follow typical meal patterns despite illness, or perhaps a determination to maintain a sense of normalcy in the domain of usual eating habits.

Food categories labeled 'milk' and 'fruit' have repeatedly defined diet patterns and have been identified as robust cluster separators, though the energy contribution from these food categories was notably higher in our patients than in comparable healthy populations[23-25]. "Fruit and White Bread" pattern also far exceeded the mean energy contribution reported for other 'high fruit' diet patterns observed in healthy populations[24]. Individuals eating the "Milk and Soup Liquid" pattern reported a larger proportion of energy from soup than reported in other populations, though the preferred consumption of soups has been described in elderly populations receiving home-delivered meals[47]. High soup intake may be related to the relative ease of preparation and consumption, or the desire for 'comfort foods' during times of illness[48]. Individuals following this pattern also had a very high proportion of total energy as milk, with values similar to "high milk" diet patterns reported in healthy populations of comparable age[23,24,26]. The elevated energy contribution from the milk category is interesting given the regular use of reduced-fat dairy products by the majority of individuals following this dietary pattern. The frequent use of reduced - fat products and high intakes of foods typically low in fat, such as fruit and white bread, seem paradoxical among individuals who are generally failing to meet energy requirements. Although the determinants of these dietary pattern remain to be elucidated, such food choices may be prompted by a desire to more closely follow dietary recommendations for healthy eating and cancer prevention[49], which in this case are not appropriate. Notably, none of the patients appeared to be consuming products specifically engineered to raise energy (ie high fat) and protein intakes.

We were able to identify groups of individuals at higher risk for malnutrition determined by specific nutrient intakes and prevalence of weight loss. Mean total caloric intake was less than estimated minimum requirements for two of the three dietary patterns, specifically those that showed greater departure from typical patterns of intake in healthy populations of the same age. The mean protein and energy intake for the "Fruit and White Bread" group fell well below the minimum recommended amounts[43]. A higher proportion of individuals in both the "Milk and Soup Liquid" and "Fruit and White Bread" diet patterns were experiencing weight loss relative to the "Meat and Potato Traditional" pattern. In addition to the 3 distinctive dietary patterns, select individuals reported dietary behaviors that were highly divergent from the population means; some reported the adoption of strict dietary regimens that greatly restricted food selection, such as a diet based almost entirely on fruit juice or a macrobiotic diet. These eating behaviors placed the individuals at especially high risk for protein-energy malnutrition. The origins of the observed eating behaviors are unknown. Dietary change and food choice may be motivated by a desire to control the cancer or prevent recurrence[49-51]. The presence and intensity of various symptoms such as pain, chronic nausea, chemosensory abnormalities, constipation, early satiety, fatigue, anxiety and depression[19,52-56], are likely to affect food selection[19,52]. Further investigation is required to explore these relationships.

Many researchers have previously reported weight loss and low energy intake to be negative prognostic indicators in patients with terminal cancer[57-59]. In this study, a small sample size may have limited our ability to detect statistical differences, as we were not able to identify any relationship between total caloric intake, frequency of eating or dietary pattern derived from cluster analysis and proximity to death.

3.4.4 IMPLICATIONS FOR ANOREXIA-CACHEXIA THERAPY

The studied subjects corresponded to the inclusion criteria of a number of recent large clinical trials of cancer cachexia intervention[7-16,60]. Typical inclusion criteria include: a history of recent weight loss, significant self-reported anorexia, affected by a range of solid tumors, an average life expectancy of 6-7 months, and capable of oral food intake.

The stated objective of the majority of anorexia-cachexia therapies is the maintenance or gain of weight and lean body mass[2]. Our data suggest that the current diet of patients with advanced malignancy may introduce a large degree of variability in study populations and in ability of patients to respond to such treatments. Net protein deposition requires a sufficient quality and quantity of dietary protein to achieve this end, and the fact that estimated energy and protein intakes are well below estimated requirements makes it less possible or impossible to realize this aim. Orexigenic therapies could not be expected to induce weight gain in the lowest intake quartile unless such agents were capable of doubling or tripling voluntary intakes and reach levels necessary to develop positive energy and N balance. It is hard to imagine that any therapy would result in gain of lean mass under conditions, for example, where the food being ingested has very low energy and protein density, such as macrobiotic or largely fruit-based diets. In recent studies such as that of Jatoi et al[8], 60% of patients failed to gain weight in response to megestrol acetate or to the provision of an enteral nutritional formula, and the heterogeneity and level of dietary intakes may help explain these treatment failures.

Our results suggest the foods consumed by advanced cancer patients correspond largely to typical foods eaten by healthy people. Supplements such as Ensure® (Abbott Laboratories) or Boost® (Mead Johnson Nutritionals) were not selected by a large fraction (70%) of patients who were living at home and making food selections according to personal/family preference. Several recent large clinical trials have used oral liquid supplements in the treatment of cancer cachexia[12,13,61,62]. These research investigations encouraged intake of about 480mL of this type of product/day; this would likely not only introduce a food product not otherwise selected by these patients, but may also displace a large fraction of other food intake. Liquid oral supplementation has been shown to significantly reduce energy derived from habitual diet in a population of frail elderly such that total caloric intake was not improved; both the volume and nutrient content of the supplement contributed to the decline in usual food intake[63]. Other forms of nutrient supplementation may be worthy of exploration, such as nutrient augmentation of foods that are habitually consumed. By contrast a subset of our subjects (30%)

selected commercial liquid supplements and obtained a significant amount of total energy and protein from them. The basis of this preference remains to be determined (convenience, ease of swallowing, nutrient density). For these individuals enteral formulae may be an appropriate vehicle for energy and protein supplementation.

The results presented provide a basis for understanding current food selection, nutrient intake and future dietary supplementation in patients with advanced cancer. The dietary patterns may help in the development of specific recommendations for overall dietary improvement, and in the identification of foods that might be well accepted by the population and that could potentially act as vehicles for nutrient supplementation.

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CHAPTER FOUR

4.0 CHEMOSENSORY ABNORMALITIES IN PATIENTS WITH CANCER

The normal function of the chemosensory perceptions of taste and smell play an important role in our daily lives, providing constant interaction with our surrounding environment and enjoyment from exposure to odors or flavors we find pleasing. Though often taken for granted in modern times, the ability to detect noxious odors and perceive tastes warning of spoiled food or dangerous ingredients ensured the survival of our ancestors. In the more recent past, disorders of taste and smell were not taken seriously in the same manner as loss of sight or hearing, as they were not considered serious life-threatening handicaps[1,2]. Currently, however, there is increased recognition of the effects of taste and smell dysfunction on activities of daily living, appetite regulation, and quality of life.

It is estimated that 1.65% of American adults suffer from a chronic chemosensory impairment[3]. While the gradual loss of chemosensory acuity is a function of normal aging[4,5], additional causes of taste and smell abnormalities include head injury[6], HIV/AIDS[7-9], liver disease[10], renal disease[11], medications[5] and cancer[12-19]; it is estimated that between one quarter and one half of all cancer patients experience changes to chemosensory perception[20]. This review will describe basic chemosensory function and methodologies for its evaluation, and will focus on chemosensory alterations described in patients with cancer. Specific chemosensory abnormalities unique to this group will be discussed along with the effects of chemosensory dysfunction on food intake, nutritional status and quality of life.

4.1 NORMAL TASTE AND SMELL FUNCTION

In order to understand chemosensory dysfunction, one must first familiarize oneself with normal taste and smell perception. Traditionally, the sensation of taste has been limited to what are considered to be the four basic taste qualities: sweet, salty, sour and bitter. However, researchers argue the existence of additional 'primary' taste quality named 'umami', which is the savory sensation caused by monosodium glutamate[21]. Taste sensation is mediated through the taste buds, the structures in which the taste receptor cells are located. Situated in the oral cavity, taste buds can be found on the tongue, soft palate, pharynx, larynx epiglottis, uvula and upper third of the esophagus[5]. Depending on their location, taste buds may be innervated by the seventh, ninth or tenth cranial nerves, through which sensory information is carried to the areas of the brain related to maintenance of homeostasis and feeding behaviour[2,5,22]. The opening of the taste bud is called the taste pore, the size of which is controlled by a gate-keeper protein[23]. Within the taste pore lie the taste receptor cells that detect and relay gustatory stimuli. Tastants, chemical stimuli, travel in solution through the taste pore of the taste bud and are detected by the taste receptor cells, which send nerve impulses to the brain coding the quality and intensity of the gustatory stimuli. Taste buds have a lifespan of 10-11 days[4]; the continual renewal of these structures makes them vulnerable to malnutrition as well as medications and other factors affecting cellular turnover.

The sense of smell is mediated by specialized receptors found in the olfactory membrane located in the nostrils. Olfactory receptor cells also undergo frequent renewal and have a lifespan of approximately 30 days[8]. At this point there is no universally accepted identification or classification of basic smell qualities[1]; the range of qualities perceived through olfaction is seemingly boundless.

The sensation of flavor is a result of the interaction between chemical stimulation of the taste and olfactory receptor cells along with the food's texture and temperature. Chewing is important in flavor perception, as it moves food around the mouth delivering taste stimuli to taste buds located on the oral surfaces while releasing volatile compounds which are perceived retronasally by the olfactory receptors. Each of these sensory modalities is stimulated independently to produce a distinct flavor when food enters the mouth. Olfaction is an extremely important component of flavor sensation and food enjoyment; in many cases, it is the characteristic mixture of specific odorants within a food that defines a food's signature 'flavor'[2]. Common examples of this include strawberry and chocolate, though it applies to most foods. Oftentimes what is perceived as a taste defect is truly a primary defect in olfaction.

4.2 TASTE AND SMELL DYSFUNCTION

Disorders of taste and smell are generally grouped into the following classifications of chemosensory dysfunction: hypogeusia (diminished sense of taste), hypergeusia (increased sense of taste), ageusia (absent sense of taste), dysgeusia (distorted sense of taste), hyposmia (diminished sense of smell), hyperosmia (heightened sense of smell), ageusia (absent sense of smell), and dysgeusia (distorted sense of smell)[4]. Abnormalities may affect some or all taste and smell qualities, or may be specific to a particular odor or tastant. For example, one might experience a diminished sensitivity to sweet stimuli without displaying abnormal acuity for salty, sour and bitter tastants. Because of the key role odor perception plays in flavor sensation, individuals complaining that foods 'have no taste' or 'taste unusual' may actually be suffering from olfactory disturbances rather than a true gustatory problem.

4.2.1 ASSESSING CHEMOSENSORY FUNCTION

4.2.1a CLINICAL MEASURES

Typically, assessment of chemosensory dysfunction is performed in a controlled environment using threshold and identification testing techniques[21,24]. For clinical evaluation of olfactory function, the subject's threshold of odor detection and odor identification are determined. These are defined as the lowest concentration of stimulus at which the subject can identify a solution as smelling different from water, and the ability of the subject to correctly identify odor stimulants[25], respectively. Similarly, thresholds of taste detection and recognition are used to measure gustatory ability. The detection threshold is the lowest concentration of stimulus at which the subject can identify a solution as tasting different from water; the recognition threshold is the lowest concentration at which the subject can correctly identify the stimulus as salty, sour, bitter or sweet[21,26]. Whole mouth methodologies, rather than regional testing procedures, are typically used to assess 'real world' gustatory function as these more closely replicate sensory responses to foods[27].

In the 1960s and 1970s, thresholds were determined according to the forced-choice stimulus drop technique described by Henkin et al[26]. The technique involves placing three drops in sequence into the oral cavity; two of these are water and one is a tastant dissolved in water. The concentration of the tastant solution is progressively increased; for each triad the subject must indicate which drop contains the taste stimulus. The lowest concentration of tastant at which the subject correctly distinguishes as being different from water is typically labeled as the detection threshold. Salivary adaptation and size of the tongue area stimulated by the solution can influence the threshold assessment, and therefore these tests can be highly variable[28]. Though use of this method is widely reported in the medical literature[12-14,29], this test is generally considered by sensory scientists to be unreliable due to these procedural limitations.

The currently accepted method for determining gustatory and olfactory taste thresholds is the three alternative forced-choice (3-AFC) ascending series method of limits technique[30,31]. As with the forced-choice three stimulus drop technique, the subject is presented with three samples; the samples are provided in small cups, two containing water and one containing a solution of tastant. Again, with each triad the subject is forced to indicate which sample contains the gustatory stimulus (or to identify the stimulus as salty, sweet, sour or bitter in the case of recognition threshold testing). A water rinse is provided between triads to prevent sensory adaptation. The concentration of tastant presented in the triad is provided in an ascending series; the threshold is the calculated mean of the first correctly identified concentration and the last incorrect concentration. Alternatively, some researchers use the concentration of the tastant solution at the first correct identification as the empirical threshold[21]. Though either threshold determination method is acceptable, the method used should be reported in the literature along with other methodological considerations.

Electrical gustometry, which involves electrical stimulation of the taste receptor cell, has also been used to measure detection thresholds, though the relationship to subjective taste abnormalities is not clear[32,33]. It is important to note that electrical hypogeusia, as determined via the electrugustometer, is not equivalent to clinical hypogeusia, and that electrically measured abnormalities do not imply that a patient will experience changes in taste perception. Furthermore, there is poor correlation between chemically and electrically derived taste sensation[34], making comparison between these methodologies difficult.

4.2.1b SELF-ASSESSMENT OF CHEMOSENSORY FUNCTION

One may experience subjective changes in taste and/or odor sensation without demonstrating significant changes in the measured thresholds, and vice versa[4]. This is true for all methods of threshold testing. Furthermore, changes in these measured thresholds, whether measured chemically or electrically, do not consistently detect changes in the perception of taste and odor intensity at concentrations exceeding those used in thresholds testing[2]. It is generally these suprathreshold ranges of taste and odor intensity in which tastants and volatiles typically appear in foods[2], and sensory alterations within these ranges may greatly affect one's ability to distinguish between different quality stimuli.

Though standardized methodologies for objective measurements of taste and smell abnormalities do exist[30,31], at this time clinically practical and convenient options for use in vulnerable populations are limited. Physical testing can be energy intensive and potentially exhausting for weak individuals. In addition, a relatively high cognitive ability is required to accurately report sensory stimulation, thus restricting the populations on whom this type of testing may be conducted. Such limitations make collecting objective measurements of chemosensory ability in a population of advanced cancer patients a challenging task, as these individuals tend to be frail, polysymptomatic and quick to fatigue.

Increasingly, questionnaires addressing self-perceived changes in chemosensory perception are employed in studies investigating the effects of subjective taste and smell abnormalities on food intake, food enjoyment, nutritional status and quality of life[9,35-38]. Testing of such questionnaires has demonstrated good validity and reliability, with strong agreement to related outcome measures such as smell identification tests, energy intake and nutritional status in the elderly[35,36] and quality of life in patients with HIV[9]. The use of questionnaires evaluating self-perceived chemosensory perception is a useful and viable option for investigating the relationship between taste and smell abnormalities and nutrition outcomes in vulnerable populations for whom physical testing may not be possible.

4.3 CHEMOSENSORY PERCEPTION AND APPETITE, FOOD INTAKE, NUTRITIONAL STATUS AND QUALITY OF LIFE

The proper function and interaction of taste and smell drive flavor perception and food palatability, affecting one's hedonic evaluation and overall enjoyment of food[39], and encouraging food intake[4,40]. Taste and smell stimuli modulate the amount of food that is eaten and the size of meals as they are involved in the initiation and termination of ingestion[41]. Chemosensory perception also plays an important role in normal digestive function, activating the cephalic phase response which triggers salivary, gastric, pancreatic and intestinal secretions involved in food digestion, gastric contractions, and intestinal motility[4,42-45]. As such, abnormalities in taste and smell perception can have a profound impact on appetite, dietary intake, nutritional status and quality of life.

4.3.1 *ABNORMAL CHEMOSENSORY PERCEPTION AND APPETITE*

Perceived abnormalities in taste and smell are known to affect the palatability of food, defined as the 'hedonic evaluation of sensory factors [of a food] such as taste and smell'[39]. Food palatability can influence one's appetite and general desire for food[12,46-48], as well as overall food intake[46,47,49-53]. A relationship between altered chemosensory function and diminished appetite has consistently been reported in the elderly and in patients with cancer, liver disease and clinical dysgeusia[10,13,40,47,48]; a similar relationship has been established for caloric intake[40,49,54]. Mattes-Kulig and Henkin[49] compared the energy and nutrient consumption of 65 persons with dysgeusia of varying etiology against that of 37 normal healthy volunteers and found that increasing degree of chemosensory impairment was significantly related to decreased energy intake. DeWys[54] reported a study in which a series of 40 cancer patients with varying malignancies were evaluated for changes in taste sensation and changes in food intake patterns. Patients were asked to provide a five-day food record, from which an estimate of overall caloric intake (in kcal/kg) was determined. The majority of patients equated reduced taste sensation with a general reduction in appetite, and when compared to the asymptomatic individuals, patients with taste abnormalities were found to have a significantly lower caloric intake ($p<0.02$). The author related this decline in intake to the decreased hedonic value of foods and changes in physiological digestive responses to the food, as discussed above.

4.3.2 *ABNORMAL CHEMOSENSORY PERCEPTION AND FOOD CHOICE*

In addition to their general effects on appetite and overall caloric intake, taste abnormalities have been shown to have more specific influences on food choices and food intake behavior[2,9,10,13,38,47,55,56]. Numerous researchers[2,57,58] have found that dietary variety is limited in individuals with poor or altered chemosensory function, placing them at higher risk for malnutrition. Ames et al[56] observed a significant relationship between perception of suprathreshold taste intensities and diet in a sub-group of mastectomized breast cancer patients with low energy intakes and high risk for malnutrition. In their assessment of dietary habits of individuals with various chemosensory disorders, Mattes-Kulig and Henkin[49] found that patients with severe dysgeusia ate considerably less fruits and vegetables than other patients with altered chemosensory function and healthy controls. Huldij et al[38] studied the relationship between appreciation for basic tastes and that of specific foods. 94 patients receiving cancer therapy were asked by means of a questionnaire to express their appreciation of the four primary tastes and a list of food items. The investigators reported that there was a significant decrease in the appreciation for bitter taste, and significant changes in the appreciation of coffee, yoghurt, buttermilk, fried and boiled chicken and boiled fish. The authors concluded that cancer patients experiencing taste aberrations due to therapy might also experience changes in their patterns of food appreciation, which may in turn affect specific food choices and overall food preferences. DeWys and Walters[13] related specific taste changes to specific food aversions and food choices. The investigators found that patients with decreased urea (bitter) recognition thresholds were more likely to report an aversion to meat and other protein foods, while those subjectively complaining of decreased taste sensitivity were more likely to prefer highly seasoned foods and to increase the amount of sugar added to foods. While findings of this sort are important for the derivation of nutritional counseling strategies, it is important to recognize that the interplay between taste and smell sensation and dietary behavior is multifaceted, and that compensatory changes are likely to result in complex and highly individual dietary changes[47].

4.3.3 ABNORMAL CHEMOSENSORY PERCEPTION AND NUTRITIONAL STATUS

The effects of chemosensory abnormality on appetite, food intake and food choice can greatly impact nutritional status. Mattes-Kulig and Henkin[49] found a significant relationship between dysgeusia and nutritional risk, as determined by the presence of one or more of the following nutritional indices: (a) acute weight loss of more than 5% usual body weight, (b) body weight <90% ideal body weight, (c) triceps skinfold measurement <15th percentile, and/or (d) arm muscle circumference <15th percentile. Nutritional risk increased with dysgeusia severity[49]. Weight loss is a common finding among individuals suffering from altered taste and smell function[13,59-61]. In a sample of 60 patients diagnosed with gustatory dysfunction of various pathologies, Markley et al[61] found a significant relationship between severity of dysgeusia and weight loss. When patients with the additional diagnosis of cancer were included in the analysis this relationship was further strengthened. While investigating the prevalence and effects of taste abnormalities in cancer patients, DeWys and Walters[13] reported a correlation between altered taste thresholds and weight loss; 16 of 17 individuals demonstrating abnormal taste thresholds had experienced a weight loss of over 2.3kg in the 2 months prior to testing. A similar relationship was demonstrated in a group of 254 cancer patients[59]; chemosensory abnormalities were significantly more prevalent among patients experiencing weight loss versus those who were not.

4.3.4 *ABNORMAL CHEMOSENSORY PERCEPTION AND QUALITY OF LIFE*

Disruptions in chemosensory perception can affect overall food enjoyment[47,62,63] and have a significant impact on quality of life[9,63-67]. The socialization of mealtimes and eating can be diminished as food becomes less pleasing, and tensions can arise if foods prepared by the caregiver are rejected[68]. In a study of 345 patients with olfactory impairment, greater than 25% reported 'enjoying life less than they used to' as a result of the olfactory abnormality[63]. Heald et al[9] studied the effect of self-perceived chemosensory complaints on quality of life in 207 HIV-infected patients. Even after controlling for CD4 cell count, HIV-1 viral load, number of AIDS diagnoses and number of medications taken, chemosensory distortions were associated with decreased quality of life in all measured domains including general health perception, physical function, role function, social function, and health distress.

The relationship between abnormal chemosensory function and quality of life has been explored in patients with cancer. Johnson[64] describes the symptomology of taste change in a 90-year-old end-stage pancreatic cancer patient. Of her reported symptoms, the patient listed dysgeusia and hypogeusia as the most distressing. For this patient, food was associated with socialization, and eating was associated with living; as a result the taste changes and subsequent inability to eat were perceived by the patient to be 'life-threatening', and had a severe impact on her overall well-being. In a study of 284 cancer patients receiving radiation therapy, Wickham et al[67] found that taste changes were associated with negative effects on quality of life, inasmuch as the patient related them to decreased food enjoyment, decreased appetite, weight loss, nausea and limitations to family interaction. The physical well-being, functional well-being and total quality of life constructs of the quality of life assessment showed significantly lower scores in patients with taste changes, versus those not experiencing this symptom. In addition, depression was twice as prevalent among patients stating that taste changes had affected their lives, compared to those who felt that taste alterations had not affected their lives. Diagnosis of taste and smell abnormalities is particularly important in the palliative care setting, where quality of life and control of distressing symptoms are of utmost priority in patient care.

4.4 ALTERED TASTE AND SMELL PERCEPTION AND CANCER

Abnormalities in taste and/or smell perception are estimated to occur in between a quarter and one half of all cancer patients[20], though such figures may be underestimated as this symptom is not often volunteered or routinely inquired after in typical oncology consultations[23]. Such chemosensory changes are considered to be the result of host responses to the disease process, cancer therapies, or a combination of the two. For patients suffering from incurable neoplastic disease, the effect of taste abnormalities on nutrient intake may be an important contributor to the patient's prognosis and overall quality of life.

4.4.1 ALTERED CHEMOSENSORY PERCEPTION IN THE CANCER PATIENT: A SENSORY PROFILE

Numerous researchers have studied chemosensory changes in patients with cancer receiving no anti-tumor therapy, with varying results (Table 4.1). Abnormalities in taste perception in which patients show an elevated or reduced threshold for all tastants have been related to a number of disease states[2,4,69] and pharmaceutical products[4,70]. A more unique chemosensory profile has been identified in a number of cancer patients prior to radiation or pharmaceutical therapeutic interventions, suggesting that the alterations in chemosensation may be directly related to the disease process rather than the medical interventions used to treat the disease. DeWys and Walters[13] studied the taste acuity in 40 cancer patients with varying malignancies. Using the forced-choice three-stimulus drop technique, detection and recognition thresholds for salt, sweet, sour and bitter tastes were determined. The median detection thresholds for salt and bitter were essentially similar in the cancer and control groups, while the median detection threshold for sweet and sour had a slight upward skew in the cancer group. The results of the recognition testing provided more interesting results. The data indicated the existence of a subpopulation of individuals among the neoplastic group with an increased recognition threshold specific for sucrose (sweet) and/or decreased recognition threshold specific to urea (bitter). Other researchers investigating the nature of altered taste perception in cancer patients have found similar results[14,19]. No other disease state has shown a similar chemosensory profile with these isolated sensory changes. Attempts to reproduce these finding have been elusive (Table 4.1), though tastant-specific abnormalities have consistently been observed[12-15,18,19]. Repeatedly, increased detection and recognition thresholds have been observed for sweet[12-14,19] and subjective reports frequently make reference to this specific decline in sensory acuity[64].

Using electrical gustometry, Ovesen et al[17] found that electrogustometric taste detection thresholds were significantly higher in patients with cancer than in age-matched controls, and concluded that the disease process increased taste thresholds in general. However, the electrogustometric measurement technique does not discriminate between the basic tastes, and therefore would not be expected to detect the same alterations in taste reported by DeWys and Walters[13].

Table 4.1 Results of threshold tests of gustation on patients with various types of cancer prior to therapy.

		Results							
		Detection Thresholds				**Recognition Thresholds**			
Study	**Cancer Type**	**Sweet**	**Sour**	**Salty**	**Bitter**	**Sweet**	**Sour**	**Salty**	**Bitter**
Carson & Gormican[12]	Breast, Colon vs Control	↑	↔	↑	↔	↑	↔	↑	↔
DeWys & Walters[13]	Various metastatic vs Control	↑	↑	↔	↔	↑	↑	↔	↓*
Gallagher & Tweedle[14]	Various vs Control	-	-	-	-	↑	↔	↔	↓
Hall et al[15]	Gastrointestinal vs Control	-	-	-	-	↔	↔	↔	↓
Kamath et al[16]	Esophageal vs Control	↔	↔	↔	↔	↔	↔	↔	↔
Pattison et al[18]	End stage vs Control†	↔	↔	↔	↓	↔	↔	↔	↓
Williams & Cohen[19]	Lung vs Control	-	-	-	-	↔ ↑*	↓	↔	↔ ↓*
Ovesen et al[17]	Lung, Ovarian, Breast vs Control	↑‡				-	-	-	-

↑ indicates increased detection/recognition threshold and therefore decreased sensory acuity
↓ indicates decreased detection/recognition threshold and therefore increased sensory acuity
↔ indicates unchanged detection/recognition threshold relative to controls
- indicates that this test was not performed in the study described

* *For a subset of subjects*

† *Increased odor discrimination suggesting enhanced olfactory acuity*

‡ *Discrimination among tastants is not possible with this type of testing*

Differences in the observed thresholds may be related in part to the methodologies used to measure taste acuity in the cancer population. The majority of work in the cancer population was performed in the 1970s and 1980s, when the forced-choice three stimulus drop technique was widely used and accepted. As discussed, the three-stimulus drop technique can produce varying results depending on the area of the tongue contacted by the stimulus and the degree of sensory adaptation. Controlling the size of the 'drop' can be difficult[17]. This method is generally considered to be outdated by current ASTM[30] and ISO standards[31]. To date, there have been no investigations to determine recognition thresholds and/or detection thresholds in cancer patients using the forced-choice ascending series methodology, which is the currently accepted standard chemosensory threshold measurement technique.

In addition to abnormalities in taste sensitivity, cancer patients often complain of olfactory disturbances. Anecdotal reports of 'phantom odors' and of heightened sensitivity to perfume and food smells are common[18]. Pattison et al[18] found that patients with advanced cancer demonstrated an increased ability to discriminate among odors compared to age-matched controls, suggesting enhanced olfactory sensation. As with taste abnormalities, altered smell perception can affect food choice and caloric intake[71], but the relationship between olfaction and caloric intake has not been adequately explored and is not widely reported in the literature.

4.4.2 POTENTIAL CAUSES OF THE ALTERED TASTE PERCEPTION IN CANCER PATIENTS

Aside from taste abnormalities related to cancers of the oral cavity and cancer therapies, the effect of cancer on taste is not fully understood. As previously discussed, the taste abnormalities reported by cancer patients are unique in comparison to those reported by other patient populations. It is well recognized that changes in taste perception may occur irrespective of the location of the primary tumor or the therapeutic interventions, suggesting that the abnormal sensory profile results from a complex interaction between numerous factors of both host and tumor origin.

Given that sensory receptor cells involved in gustation and olfaction may be particularly susceptible to changes in nutrient supply due to their relatively high turnover rate[4], general undernutrition has been investigated as a possible mediator of taste abnormalities in the cancer patient. In particular, specific deficiency states of protein and zinc have been studied for their potential role in the taste alterations reported in cancer patients.

Protein deficiency might be expected to have significant effects on taste acuity in individuals with increased protein requirements and increased protein turnover. It is well recognized that aberrant metabolic processes, including increased protein turnover, are common among patients with cancer[72]. In such a case, protein deficiency might impair taste bud regeneration and therefore reduce general flavor perception. However, protein malnutrition has not been related to specific alterations in taste acuity[69], and as such cannot fully explain the taste abnormalities present in the cancer population.

Zinc is known to play an important role in the normal function of taste receptors[29], and as such has been investigated in relation to the taste abnormalities observed in cancer patients. Alterations in circulating serum and/or salivary zinc levels may induce conformational changes in the protein that controls the diameter and permeability of the taste bud pore[29], which affects the quantity of stimulus required for sensory perception and response. Through this mechanism, reductions in circulating levels of zinc may effectively raise detection thresholds of all tastants[29]. While low plasma zinc concentrations have been related to decreased taste sensation, zinc levels have not been related to degree of taste impairment[69]. In addition, plasma zinc concentrations are highly susceptible to the metabolic response that occurs in response to infection, injury and neoplastic disease[73], making zinc status difficult to measure. As a result, the effects of zinc status on taste acuity may be difficult to interpret in patients experiencing a sustained inflammatory response.

When nutrient deficiency has been studied in relation to taste sensation, no single nutrient has been identified as the sole contributing factor. Furthermore, the taste abnormalities observed in non-cancer patients with various micronutrient and/or macronutrient deficiencies have been associated with taste changes resulting in an overall decline in taste sensation[69]. Alternatively, the taste alterations seen in cancer patients often involve a decreased acuity for sweet and a simultaneous increased acuity for bitter tastes, while sensitivity to salty and sour remain relatively unchanged[13]. This unique profile suggests that in cancer patients, the condition is not simply the result of a nutrient deficiency hypogeusia, but rather a complex host response to malignancy manifesting as simultaneous hypogeusia and dysgeusia.

Numerous mechanisms for the hypersensitivity to bitter taste have been proposed. DeWys[74] hypothesized that altered levels of circulating amino acids, which are known to elicit bitter tastes, might provide subthreshold stimulation of the taste buds resulting in a lowered taste threshold for bitter tastes. The elevated protein turnover that is commonly present among cachectic cancer patients may be expected to significantly alter the levels of circulating amino acids[29,69]. However, DeWys and Walters[13] were unable to identify a correlation between blood urea nitrogen (BUN) or blood uric acid measurement and decreased bitter threshold in cancer patients, suggesting that altered amino acid blood chemistry is not in itself responsible for the lowered threshold to bitter tastes. Similarly, Kamath et al[16] were not able to establish a relationship between bitter recognition thresholds and salivary urea concentrations in patients with cancer of the esophagus.

Ovesen et al[32] compared recognition thresholds for the four basic tastes in 27 patients with small-cell lung cancer versus 22 weight-matched controls with non-malignant diseases using the forced-choice three stimulus drop technique. Though no significant differences were observed between cancer patients and controls, weight-losing individuals had a significantly increased taste sensitivity to bitter than weight-stable counterparts, suggesting that weight loss itself may be a factor in altered bitter thresholds. An alternative theory is that the observed weight loss was the result of circulating catabolic factors that affected taste thresholds while accelerating tissue losses.

It has been known for some time that cytokines and acute-phase proteins, which are ubiquitous in circumstances of sustained inflammatory response, have the ability to activate gustatory afferents, which can induce sensitization of taste receptors and lead to alterations in taste perception[75,76]. In cachectic cancer patients, the metabolic abnormalities and tissue wasting are caused in part by a chronic inflammatory response mediating the release of pro-inflammatory cytokines and acute-phase proteins[77]. It has been proposed that these pro-inflammatory factors may be involved in the dysgeusia reported by some cancer patients[69]. Pattison et al[18] studied the relationship between taste acuity and inflammatory response in end-stage cancer patients using the three-stimulus drop technique. The authors found that patients with decreased taste threshold for bitter had higher levels of the acute-phase protein C-reactive protein. In addition, patients with the lowest bitter thresholds were found to have the highest levels of tumor necrosis factor-α (TNF-α). The results indicate that these mediators of catabolism may also be related in part to the heightened sensitivity to bitter taste that is associated with cancer patients. Interestingly, the sensory-altering activity of these pro-inflammatory products has not been investigated in other patient populations suffering from sustained inflammatory response.

While several mechanisms have been proposed as potential mediators of the altered chemosensation in cancer patients, a single, comprehensive model providing an explanation for the specific abnormalities seen in this population has yet to be found. It is believed that the taste abnormalities associated with malignancy may well be the consequence of a complex interaction between a nutrient deficiency state, and inflammatory and metabolic processes occurring within the patient in response to neoplastic growth.

4.4.3 ALTERED TASTE PERCEPTION RELATED TO CANCER THERAPY

While the described taste abnormalities may be present in the cancer patient at the time of diagnosis and prior to initiation of any cancer therapy[68], therapeutic interventions such as radiation and chemotherapy are known to induce alterations in taste function both in patients with and without this symptom[29].

Decreased taste acuity is a common symptom among patients receiving radiation to the head and neck region. Mossman et al[78] measured the changes in taste acuity in 27 cancer patients receiving radiation to the head and neck region. Taste acuity was measured for four taste qualities by the forced-choice three drop technique and a forced scaling technique, which measured taste intensity responsiveness. In 18 of the patients, taste thresholds were measured before, during and after irradiation treatment. The investigators found that some degree of clinical taste impairment was present in 93% of the patients prior to radiation therapy, though only 17% were subjectively aware of the impairment. Characterization of the taste impairment in this patient group indicated that thresholds for salt, sour and bitter tastes were increased, which contradicts the findings of DeWys and Walters[13]. The result of the taste threshold testing indicates that radiation therapy further impairs taste acuity, as both measured and subjective taste impairment were reported. Interestingly, bitter and salt acuity showed the greatest impairment, and were the slowest to recover after treatment cessation. Sweet showed the lowest overall impairment.

The decreased taste acuity brought about by radiation is thought to occur for several reasons. Radiation to the head and neck region can involve the salivary glands, resulting in a decreased salivary flow and ultimately dry mouth. Since tastants must be in solution for detection to occur, dry mouth can decrease overall taste acuity by preventing these tastants from being detected. In addition, radiation to the head and neck region can damage the microvilli of the taste buds, which can further impair taste sensation. Ripamonti et al[29] have suggested that supplementation with zinc sulfate during and after irradiation treatment may have protective effects against taste impairment, and may encourage quicker recovery of normal taste function after treatment cessation.

Medicines used for cancer treatment and other conditions may also alter taste sensation, with more than 80 different medications implicated as potential perpetrators of abnormal taste sensation[5,79-81]. Boakes et al[82] indicated that 50% of 98 patients who had received at least four chemotherapy treatments had changes in their diet. Most frequently these were ascribed to alterations in taste perception, and manifested as aversions to meat and coffee. Women with breast cancer reported taste changes for beef, pork, chicken, coffee and cakes, although these changes did not account for alteration in dietary intake[83]. Medications may reduce taste acuity by inducing dry mouth or may alter taste sensation through production of 'phantom-tastes'[70]. In addition, some chemotherapeutic drugs have been shown to cause reduced smell acuity by damaging the olfactory mucosa[79,84], and as such may also affect flavor perception.

4.5 ALTERED CHEMOSENSORY PERCEPTION IN PATIENTS WITH ADVANCED CANCER

Patients with advanced cancer typically experience a myriad of symptoms that might be expected to affect food intake, nutritional status and quality of life[59,85]. Abnormalities in chemosensory function are among the most common symptoms reported by patients with advanced cancer, and are often listed as one of the most distressing for the patient and caregiver[64,68,86,87]. The anorexia associated with malignancy may be related in part to changes in taste perception, which as discussed can lead to a general reduction in the pleasurable aspect of taste and a reduction in food palatability, resulting in an overall decline in appetite and an impaired nutritional intake. The result is the continuation of a vicious cycle promoting weight loss, malnutrition and loss of functional status in patients with advanced cancer. For patients suffering from incurable neoplastic disease, the effect of taste abnormalities on nutrient intake may be an important contributor to the patient's poor prognosis and diminished quality of life.

Altered taste perception resulting from both cancer and cancer therapies are a significant problem for patients with advanced cancer. As the goal of palliative care is the minimization of symptom distress and maintenance of patient quality of life, palliation of the distressing and nutritionally disruptive symptom of chemosensory distortion should receive increased attention. Comprehensive studies using reliable up-to-date techniques are required to further investigate the nature of chemosensory disruption and the relationship between chemosensory function and quality of life in patients with advanced neoplastic disease. Information regarding olfactory function in this patient population is limited; odor threshold and odor recognition tests have not been performed. Recognizing that the application of these types of methodologies in a palliative population may prove challenging due to cognitive and frailty issues, we suggest that self-assessment questionnaires may be a suitable alternative.

The relationship between chemosensory dysfunction, nutritional status and quality of life in patients with advanced cancer is a long neglected area requiring further investigation. Because up-to-date information is lacking, current nutritional intervention strategies for the cancer population do not focus on compensation for altered sensory perception, and as such are overlooking an important component of the patient's care. Future dietary recommendations should address the sensory symptomology of the cancer patient, with the goal of improving appetite stimulation, food palatability, nutrient intake and overall quality of life.

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CHAPTER FIVE

5.0 SELF-REPORTED TASTE AND SMELL ABNORMALITIES AND THEIR RELATIONSHIP WITH FOOD INTAKE, NUTRITIONAL STATUS AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER

5.1 INTRODUCTION

Decreased appetite resulting in inadequate dietary intake is a significant factor involved in the weight loss and progressive functional decline associated with advanced cancer; in fact, anorexia is the most consistent clinical finding in weight-losing cancer patients[1]. The anorexia associated with malignancy may be related in part to changes in chemosensory perception. The normal function of taste and smell sensation drives flavor perception and supports normal digestive function by initiating the release of digestive enzymes, and stimulating gastric contractions and intestinal motility[2-6]. Consequently, chemosensory losses and distortions can affect appetite, food preference, energy intake and ultimately, nutritional status. Furthermore, the effects of aberrant chemosensory function on appetite and food enjoyment have been shown to significantly impact quality of life[7-12].

It is estimated that between one quarter and one half of all cancer patients experience changes to their taste and/or smell perception[13]. This is likely a conservative estimate, as chemosensory abnormalities are often not addressed in routine oncology consultations and may not be volunteered by patients unless prompted[14]. The majority of chemosensory related research in cancer patients has examined the effects of anti-cancer therapies such as radiation and chemotherapy on chemosensory perception[9,12,14-17]. However, altered taste and smell sensation may be present prior to or long after active cancer therapy[18-25], and this symptom is frequently cited among patients with advanced cancer for whom curative therapies have been discontinued in favor of palliative care[8]. It is currently unknown what proportion of these patients with advanced cancer experience taste and smell defects, or how these changes affect nutrient intake, food preference, nutritional status and quality of life. The focus of palliative care is to minimize patient symptom burden and optimize quality of life. For patients suffering from incurable neoplastic disease, the effect of taste abnormalities on nutrient intake may be an important contributor to the patient's prognosis and overall quality of life.

Though abnormal taste and smell perception are likely to affect food preference and intake, current dietary recommendations and nutrition intervention strategies for patients with advanced cancer do not cater to the food preferences or sensory symptomology of this patient group. In a large cross-sectional study of dietary intake in patients with advanced cancer, we recently identified 3 dietary intake patterns differing in terms of food selection and nutrient intake; the relationship between these dietary patterns and chemosensory perception warrants further investigation. In order to develop improved methods for addressing the nutritional status and quality of life in patients with advanced cancer, the impact of chemosensory dysfunction on food intake and quality of life must be explored. The objectives of this study were to (a) determine the prevalence of taste and smell alterations in patients with terminal cancer, (b) describe the taste and smell abnormalities affecting this population, and (c) test for a relationship between self-perceived taste and smell sensation and food and nutrient intake, nutritional status and quality of life in this population.

5.2 PATIENTS AND METHODS

5.2.1 STUDY POPULATION AND DATA COLLECTION

Subjects with advanced cancer (defined as locally recurrent or metastatic, n=50) were recruited either from the Palliative Home Care program serving Edmonton, or from the Pain and Symptom clinic of the Cross Cancer Institute, a cancer treatment center serving Edmonton and northern Alberta. The study was reviewed and approved by the Alberta Cancer Board Research Ethics Board and the Health Research Ethics Board of the University of Alberta. All participants spoke English and provided written informed consent; patients suffering from oral, nasal or esophageal cancer, and patients currently receiving radiation or chemotherapy, were excluded due to the direct effects these cancers and cancer treatments can have on chemosensory perception and food intake. All subjects were resident in their homes, were physically able to consume foods and were assumed to make food choices by personal preference.

Dietary records (detailing intake for 3 consecutive days, including 1 weekend day and 2 weekdays) were used to assess subjects' energy intakes; the validity and reliability of dietary records in the estimation of current dietary intake is discussed in Chapter 3. A dietitian instructed participants on proper completion of the food record, and reviewed completed records with the study participant for accuracy and completeness.

Nutrient intakes were estimated using the Canadian Nutrient File Database of the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR). Analysis focused on energy and protein intake, and macronutrient composition of the diet (expressed as total energy contributions (% kcal) from fat, carbohydrate, and protein).

Mean energy intakes were expressed in total kcal/day and kcal/kg body weight (BW)/day. Mean protein intakes were expressed in total g protein/day and g/kg BW/day. Food attitudes and changes to food appreciation were assessed by way of a targeted interview addressing favorite foods, changes to food appreciation and meal appreciation. The determination of dietary intake patterns is described in Chapter 3. The first 32 subjects recruited to this study were included in the dietary pattern analysis; preliminary analysis of the relationship between self-perceived chemosensory function and dietary intake pattern was performed on this subset of participants.

Each subject's height and weight were measured, and in any case where a participant was bedridden or unable to stand unsupported, the most recently recorded values were taken from the patient's medical chart. History of weight loss over previous 6 months was self-reported and verified with patient's medical chart where possible.

Self-perceived taste and smell function were assessed by means of a questionnaire which has been used to evaluate chemosensory function in AIDS patients[7] and in a population of elderly individuals[26] (Appendix B). The questionnaire yields a taste complaint score (0-10) on the basis of subject responses to 9 questions addressing the following problems: self-perceived changes to the general sense of taste and to specific basic taste qualities (sweet, sour, salty, bitter), changes to the way a food tastes, presence of a bad taste in the mouth, effect of medications on the sense of taste, and self-perceived severity of taste abnormalities. The subject is given one point for each reported taste complaint and two points for a rating of 'severe' or 'incapacitating' on the severity of the taste abnormality. Similarly, a smell complaint score (0-6) was generated by adding one point for a positive response to each of 5 questions addressing self-perceived changes to the sense of smell, changes to the way a food smells, sensitivity to odors, effect of medications on the sense of smell, and self-perceived severity of smell abnormality. Two points were assigned to a rating of 'severe' or 'incapacitating' on the severity of the smell abnormality. The total chemosensory complaint score (0-16) was calculated by adding the individual taste and smell complaint scores.

A targeted interview was used to identify the presence of factors other than cancer that may influence taste and smell function, including smoking status, dentures, hay fever and/or sinusitis, and previous diagnosis of a taste or smell disorder (Appendix B).

Quality of Life (QOL) was assessed using the Functional Assessment of Anorexia/Cachexia Therapy Version 4© (Copyright David Cella, PhD) (FAACT) instrument (Appendix B), which was developed and validated to reliably measure four primary domains of global quality of life along with specific anorexia/cachexia-related quality of life issues[27]. Physical well-being (PWB), functional well-being (FWB), social/family well-being (SFWB), and emotional well-being (EWB) subscales comprise the four core measures of quality of life assessed by this tool; an additional 12-item subscale evaluates nutritional quality of life (A/CS). Responses are given using a 5-point Likert-type scale; the total FAACT© QOL score is measured on a scale of 0 to 156 and is calculated by summing the scores of the 5 individual QOL domains. Higher scores indicate better quality of life[28].

5.2.2 DATA ANALYSES

Descriptive statistics were used to determine the prevalence, quality and intensity of chemosensory abnormalities in the population studied; regression analysis was used to assess the relationship between chemosensory complaint score and energy intake. Individuals were then stratified into groups according to chemosensory complaint score; based on the distribution of the chemosensory complaint score (Figure5.1C), three separate groups were identified (Table 5.1). One-way analysis of variance was used to compare energy and protein intakes and macronutrient composition of the diet across the 3 chemosensory complaint groups. The Wilcoxon rank-sum test procedure was used to compare weight loss and quality of life scores among the 3 chemosensory complaint groups, and by separate taste and smell complaint scores. The Wilcoxon rank-sum test procedure was also used to assess the relationship between dietary intake pattern and chemosensory complaint score. All statistical analyses were performed using the Statistical Analysis System (SAS for Windows, version 8.2., 1999, SAS Institute Inc, Cary NC).

Table 5.1. Stratification of subjects based on chemosensory complaint score

Chemosensory Complaint Group	Chemosensory Complaint Score	n
No complaint	0	7
Mild to Moderate Complaints	1 to 6	22
Acute Complaints	7 to 16	21

5.3 RESULTS

Fifty patients completed the food diary, chemosensory questionnaire and FAACT© quality of life questionnaire for assessment. Characteristics of the study population are shown in Table 5.2.

Table 5.2 Characteristics of chemosensory study population

	Study Population n=50
Gender [n (%)]	
Male	19 (38)
Female	31 (62)
Age (y)	65.1 ± 12.1
Smoking status [n (%)]	
Current smoker	4 (8)
Former smoker	24 (48)
Wears dentures [n (%)]	19 (38)
Current hay fever [n (%)]	3 (6)
Current sinusitis [n (%)]	7 (14)
Previous diagnosis of taste or smell problem [n (%)]	1 (2)
Cancer Diagnosis [n (%)]	
Lung	4 (8)
GI	10 (20)
Breast	17 (34)
Prostate	3 (6)
Other	14 (28)
Primary Unknown	2 (4)

5.3.1 CHEMOSENSORY COMPLAINTS

Total chemosensory complaint scores ranged from 0 to 14 (Figure 5.1A). Only 7 of the 50 patients [14%; 95% confidence interval (CI), 4-24%] surveyed reported no chemosensory complaints of any kind, scoring 0 out of 16 for the total chemosensory complaint score. Forty-three of all subjects (86%; 95% CI, 76-96%) reported some type of subjective chemosensory abnormality. Of those, 25 (50%; 95% CI, 36-64%) had both taste and smell complaints, 15 (30%; 95% CI, 17-43%) described only taste complaints and 3 described only smell complaints (6%; 95% CI, 0-13%).

Taste complaint scores ranged from 0 to 9 (Figure 5.1B). The most common taste complaint was the existence of a persistent bad taste in the mouth, which was reported by 32 (64%) of the subjects. The frequency of positive responses to questions regarding specific taste complaints are shown in Table 5.3. Five of the 40 individuals reporting at least one taste complaint (13%; 95% CI, 4-22%) described their abnormal sense of taste as 'severe' or 'incapacitating'.

Smell complaint scores ranged from 0 to 6 (Figure 5.1C). The most common smell complaint was an abnormal sensitivity to odors, which was reported by 20 subjects (40%); 14 of these reported an increased sensitivity to odors (Table 5.3). Three of the 22 individuals reporting at least one smell complaint (14%; 95% CI 4-24%) described their abnormal sense of smell as 'severe' or 'incapacitating'.

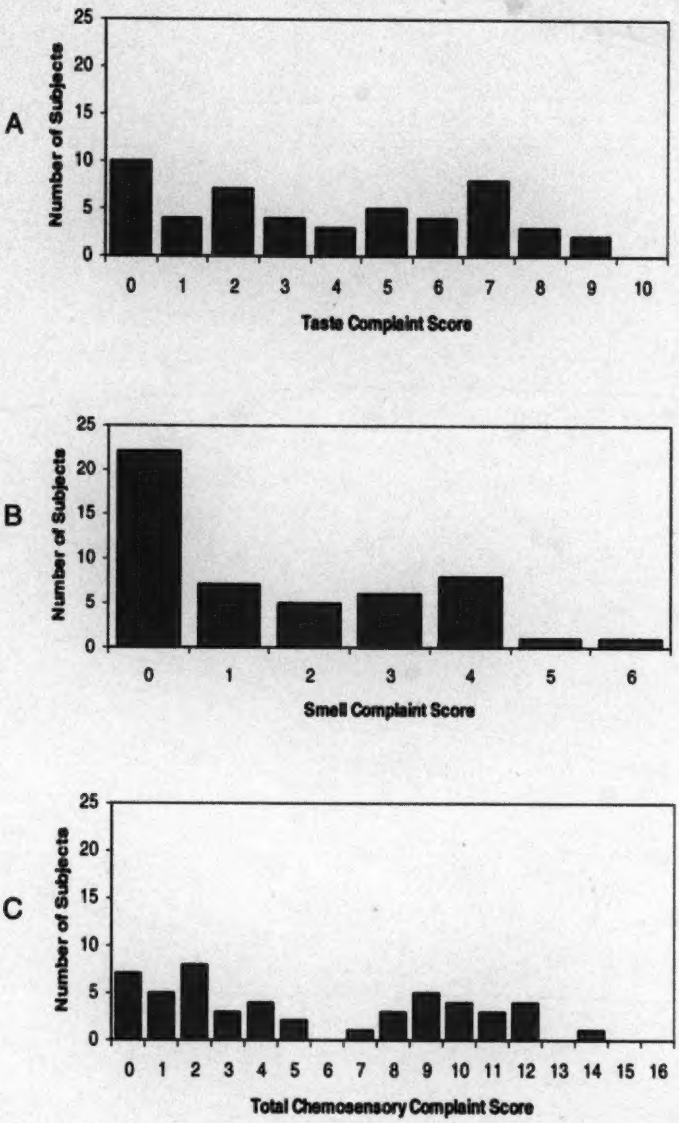


Figure 5.1 (A) Distribution of taste complaint scores, (B) Distribution of smell complaint scores, and (C) Distribution of chemosensory complaint scores for 50 patients with advanced cancer.

Table 5.3 Frequency of responses to questions addressing taste and smell abnormalities

Taste Complaint	Yes n (%)	No n (%)
I have noticed a change in my sense of taste	27 (54)	23 (46)
A food tastes different than it used to	24 (48)	26 (52)
I have a persistent bad taste in mouth	32 (64)	18 (36)
Drugs interfere with my sense of taste	9 (18)	41 (82)
I am experiencing an abnormal sensitivity to salt	19 (38)	31 (62)
Salt tastes [n (%)]:		
stronger	11 (22)	
weaker	8 (16)	
I am experiencing an abnormal sensitivity to sweet	19 (38)	31 (62)
Sweet tastes [n (%)]:		
stronger	12 (24)	
weaker	7 (14)	
I am experiencing an abnormal sensitivity to sour	16 (32)	34 (68)
Sour tastes [n (%)]:		
stronger	14 (28)	
weaker	2 (4)	
I am experiencing an abnormal sensitivity to bitter	12 (24)	38 (76)
Bitter tastes [n (%)]:		
stronger	10 (20)	
weaker	2 (4)	
I would rate my abnormal sense of taste as [n (%)]:		
insignificant	24 (48)	
mild to moderate	21 (42)	
severe to incapacitating	5 (10)	
Smell Complaint		
I have noticed a change in my sense of smell	14 (28)	36 (72)
A food smells different than it used to	15 (30)	35 (70)
Specific drugs interfere with my sense of smell	2 (4)	48 (96)
I have abnormal sensitivity to odors	20 (40)	30 (60)
odors are:		
stronger	14 (28)	
weaker	6 (12)	
I would rate my abnormal sense of smell as [n (%)]:		
insignificant	26 (52)	
mild to moderate	21 (42)	
severe to incapacitating	3 (6)	

5.3.2 CHEMOSENSORY COMPLAINTS, NUTRIENT INTAKE AND FOOD ENJOYMENT

The relationship between nutrient intake and chemosensory complaint score was assessed. Regression analysis revealed a significant negative association between chemosensory complaint score and energy intake; individuals experiencing a greater number of chemosensory abnormalities ingested significantly fewer calories (Figure 5.2, *P*=.0109, R^2=.1277). When assessed individually, both taste and smell complaint scores were inversely related to energy intake (*P*=.0322 and *P*=.0054, respectively). Individuals who rated their abnormal sense of taste as 'severe' or 'incapacitating' ate significantly fewer calories than those who rated their problem as 'insignificant' or 'moderate' (*P*=.0055).

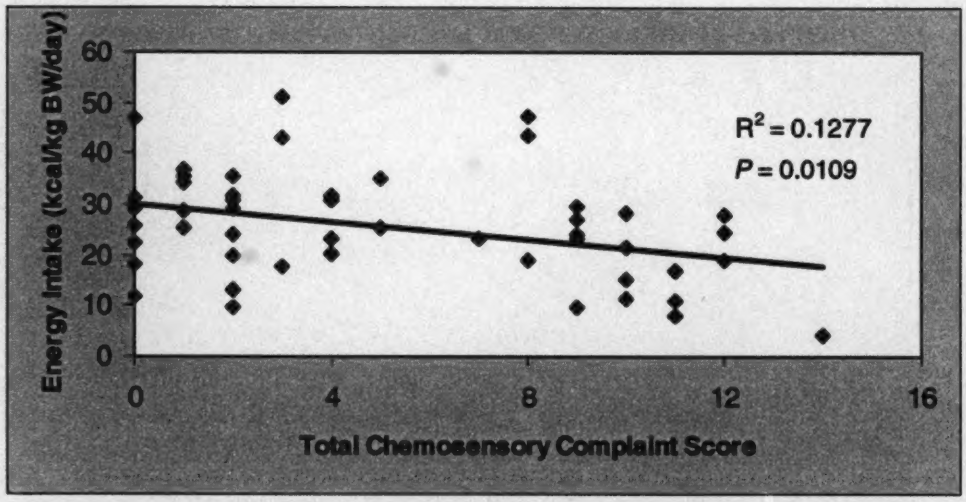
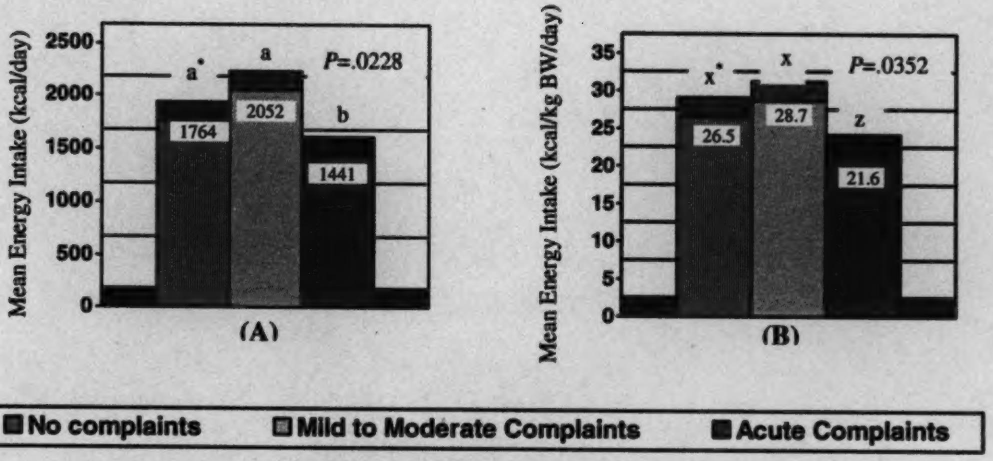


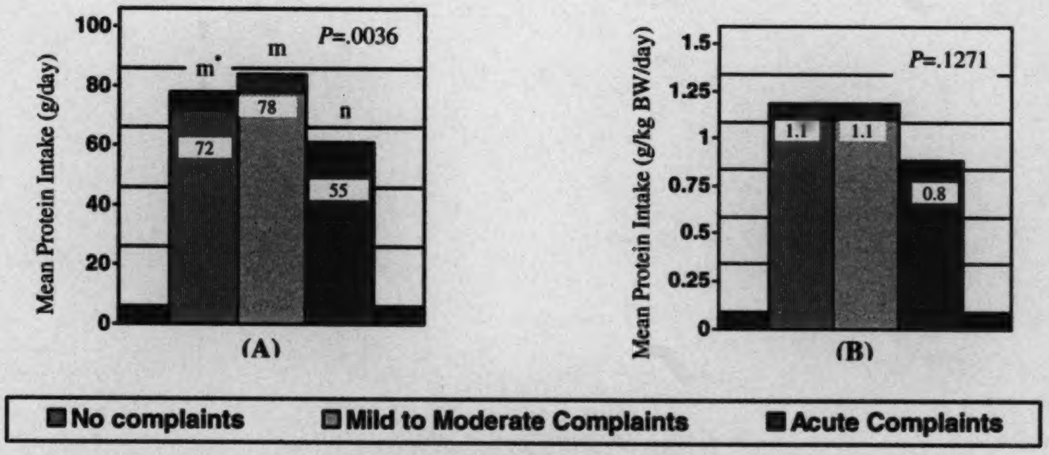
Figure 5.2 Energy intake (kcal/kg BW/day) in relation to Total Chemosensory Complaint Score

Nutrient intakes by chemosensory complaint group are shown in Figures 5.3 and 5.4 and Table 5.4. Macronutrient composition of the diet was not associated with chemosensory complaint score (Table 5.4); observed differences in protein intake among chemosensory complaint groups were associated with energy intake (*P*<.0001) and not chemosensory complaint score (*P*=.8576). Similarly, the observed differences in weight loss among chemosensory complaint groups was related to energy intake and not chemosensory complaint score (*P*=.1083).



*values marked with differing superscript indicates significant difference at α=0.05

Figure 5.3 (A) Energy intake (kcal/day) by Chemosensory Complaint Group; and (B) Energy intake (kcal/kg BW/day) by Chemosensory Complaint Group



*Differing superscripts indicate significance at α=0.05

Figure 5.4 (A) Protein intake (g/day) by Chemosensory Complaint Group; and (B) Protein intake (g/kg BW/day) by Chemosensory Complaint Group

Table 5.4 Nutrient intake by chemosensory complaint group

	Chemosensory Complaint Group								
	No Complaints		Mild to Moderate Complaints		Acute Complaints				
Nutritional Indices	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	*p*-value		*p*-value[†]
Energy Intake									
kcal/day	1764 (1820)	291	2052 (1983)	708	1441 (1398)	772	0.0228	1,2 > 3	-
kcal/kg BW/day	26.5 (25.8)	11.2	28.7 (29.9)	9.5	21.6 (21.7)	10.7	0.0352	1,2 > 3	-
Protein Intake									
g/day	72 (67)	23	78 (71)	24	55 (44)	32	0.0336	1,2 >3	0.6735 (NS)
g/kg BW/day	1.1 (1.0)	0.4	1.1 (1.1)	0.3	0.8 (0.8)	0.5	0.1271 (NS)	-	0.8576 (NS)
Energy by macronutrient									
Carbohydrate (% kcal)	51.1 (50.2)	8.6	55.8 (55.0)	6.6	57.6 (56.8)	9.1	0.1937 (NS)	-	-
Fat (% kcal)	34.9 (33.6)	7.8	30.7 (31.0)	6.6	29.2 (29.5)	7.2	0.1878 (NS)	-	-
Protein (% kcal)	15.9 (14.3)	4.5	15.4 (15.0)	3.0	15.7 (14.6)	3.9	0.9316 (NS)	-	-
% Weight loss[‡]	1.8 (0)	3.0	6.6 (0)	8.9	10.4 (8.9)	8.9	0.0171	3>1	0.1083 (NS)

[†] Adjusted for energy intake

[‡] Percent weight loss over previous 6 months

Abbreviations: SD, standard deviation; kcal, kilocalories; BW, body weight; NS, not significant at α=0.05

Food enjoyment was significantly lower among individuals with acute chemosensory complaints relative to those with no complaints or with mild to moderate chemosensory complaints (*P*=.0110); individuals with acute chemosensory complaints were also more likely to report a change in their favorite foods (*P*=.0405). All 7 individuals with no chemosensory complaints (100%) and 18 of 22 individuals with mild to moderate chemosensory complaints (82%; 95% CI, 66-98%) reported no change to their favorite foods, whereas only 4 of the 21 (19%; 95% CI, 2-36%) individuals with acute chemosensory complaints reported no change to their favorite foods. Of the 17 individuals with acute chemosensory complaints reporting a change to their favorite foods, 5 stated that they no longer had a favorite food because they were unable to enjoy any of the foods eaten. Most individuals specified a current favorite food, and though choices were highly variable, meat and potatoes, desserts, fruits and fruit juices and milk tended to be the foods reported with the highest frequency.

A significant relationship between dietary intake pattern and chemosensory complaint score was identified (P=.0308); individuals following the Milk and Soup 'Liquid' or Fruit and White Bread dietary pattern tended to have higher chemosensory complaint scores and than those following the "Traditional" Meat and Potato pattern.

5.3.3 CHEMOSENSORY COMPLAINTS AND QUALITY OF LIFE

Chemosensory complaint score was negatively associated with quality of life (Figure 5.5, *P*=.0064); in particular, the physical well-being (R^2=.2680, *P*=.0001) and anorexia-cachexia-related nutritional well-being (R^2=.3491, *P*<.0001) constructs of global quality of life were significantly associated with chemosensory complaint score. Individual taste complaint scores and smell complaint scores both showed a significant relationship with the nutrition-related quality of life domain (R^2=.3112, *P*<.0001 and R^2=.2993, *P*<.0001, respectively). Similar relationships were observed when individuals were stratified into chemosensory complaint groups on the basis of chemosensory complaint score (Table 5.5).

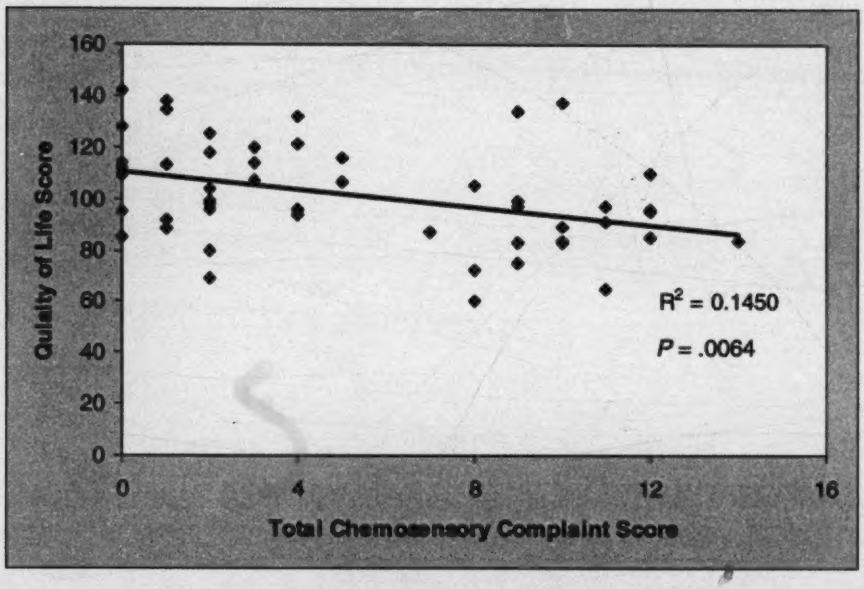


Figure 5.5 Quality of life score in relation to Total Chemosensory Complaint Score

Table 5.5 Quality of life scores by chemosensory complaint group

	Chemosensory Complaint Group						
	No Complaints		Mild to Moderate Complaints		Severe Complaints		
Quality of Life Domain	Mean (Median)	SD	Mean (Median)	SD	Mean (Median)	SD	*p*-value
Global Quality of Life	112 (111)	19	107 (107)	18	92 (89)	19	0.0070
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical Well Being	20.3 (21)	4.0	20.0 (20)	3.8	14.3 (15)	5.5	0.0020
Functional Well Being	15.3 (15)	6.8	14.6 (14)	5.1	13.5 (14)	5.5	0.6927
Social/Family Well Being	21.1 (20)	4.1	21.2 (22)	4.2	22.8 (24)	4.0	0.3682
Emotional Well Being	15.9 (15)	5.1	(16.5 (17.5)	5.2	15.2 (15)	5.4	0.5228
Anorexia-Cachexia-Related Nutritional Well Being	39.6 (39)	6.3	34.9 (34)	5.6	26.1 (27)	9.1	0.0003

5.4 DISCUSSION

This study describes self-perceived chemosensory abnormalities experienced by patients with advanced cancer who are not receiving active radiation therapy or chemotherapy. Furthermore, this study is the first to investigate the effects of these self-perceived chemosensory abnormalities on dietary intake, food enjoyment and quality of life among patients with advanced cancer who are not receiving active radiation therapy or chemotherapy. The majority of advanced cancer patients surveyed experience chemosensory abnormalities; 50% report the presence of both taste and smell dysfunction. These findings are of particular importance in this palliative population because of the effect chemosensory abnormalities can have on energy intake, food choice, food enjoyment and quality of life.

Malnutrition related to inadequate dietary intake is present in up to 90% of patients with advanced cancer, adversely affecting patient survival and quality of life[29-31]. The observed relationship between chemosensory complaints and energy intake provides evidence that individuals reporting self-perceived chemosensory disturbances are at increased risk for malnutrition. This relationship is supported by the fact that individuals with acute chemosensory complaints had lost, on average, a greater percentage of body weight than those with no complaints or mild to moderate chemosensory complaints. A similar relationship between chemosensory dysfunction and caloric intake in untreated cancer patients with varying metastatic malignancies was reported by DeWys[32]. The author suggested that the decline in dietary intake was related to a decreased hedonic value of foods and a disruption of normal physiological responses to food caused by abnormal chemosensation. Similarly, weight loss is a common finding among individuals suffering from altered taste and smell perception[19,33-36].

Due to the cross-sectional nature of this study, we cannot assess whether the reported chemosensory abnormalities caused the observed decreased energy intake, or whether they were an indicator of low intake. Given that sensory receptor cells involved in gustation and olfaction may be particularly susceptible to changes in nutrient supply due to their relatively high turnover rate[2], general undernutrition is a possible mediator of observed taste abnormalities in the cancer patient. However, the taste abnormalities observed in non-cancer patients with various micronutrient and/or macronutrient deficiencies have been associated with taste changes resulting in an overall decline in taste sensation[37], this general decline in chemosensory acuity was not typically reported by our patients. Conversely, a causal relationship between chemosensory experience and dietary intake has been established in the elderly, for whom the sensory enhancement of foods resulted in increased dietary intake[38,39] and improved functional status[40]. Furthermore, the observed relationship between chemosensory complaint score and dietary pattern suggests that self-perceived taste and smell abnormalities are related to food preference in patients with advanced cancer; individuals with high chemosensory complaint scores tended to follow dietary patterns in which the majority of calories are derived from the milk, soup, cereal, fruit, white bread and supplement food categories. This helps to identify foods that are consistently chosen and presumably preferred by individuals with a greater number of perceived chemosensory problems. These combined results suggest that dietary interventions catering to the unique chemosensory symptomology of patients with advanced cancer may result in improved dietary intake and therefore warrant further investigation.

A considerable proportion of our subjects regard their chemosensory abnormalities as being substantially disruptive and therefore clinically relevant; this was supported by the observed relationship between chemosensory complaint score and quality of life. Individuals with acute chemosensory complaints had lower scores for global quality of life, and in particular scored lower on the physical well-being and nutrition-related quality of life subscales. Furthermore, food enjoyment was significantly lower among individuals reporting acute chemosensory dysfunction. Wickam et al[12] correlated taste changes to decreased physical well-being, functional well-being and total quality of life among cancer patients receiving chemotherapy. As was observed in our sample, subjects related abnormal taste sensation to decreased food enjoyment and weight loss. Heald et al[7] studied the effect of self-perceived chemosensory complaints on quality of life in 207 HIV-infected patients and found that chemosensory distortion was associated with decreased quality of life in all measured domains, even after controlling for CD4 cell count, HIV-1 viral load, number of AIDS diagnoses and number of medications taken.

While it is unknown whether the abnormal chemosensory dysfunction reported by our subjects resulted in or merely reflected reduced quality of life, individuals in various patient populations have consistently identified chemosensory abnormalities to be particularly distressing[8,41-43]. Attempts to improve or normalize the chemosensory experience of terminal cancer patients have the potential to improve quality of life as well as nutritional status.

The reliability of self-reported chemosensory information to detect empirically measurable changes to chemosensory function has not been confirmed; a direct association between self-perceived chemosensory abnormalities and objectively measured detection and recognition thresholds has been difficult to establish[7,44,45]. The inability to identify such a relationship is likely due to the fact that objective measures of chemosensory thresholds do not accurately detect chemosensory distortions; furthermore, the complex interaction of taste stimuli and volatile flavor compounds, as experienced with food consumption, cannot be assessed through basic threshold testing. Objective tests of chemosensory function were not performed and therefore we are not able to discuss the relationship between chemosensory acuity and chemosensory complaint score in this population; however, we argue that subjective or self-perceived changes to chemosensory function are likely to provide sufficient stimulus to alter behavior regardless of whether a measurable objective abnormality exists. Rather, the sensory experience as perceived and described by the subject is likely to affect food intake behavior and quality of life. This is supported by the observed relationship between dietary intake pattern and chemosensory complaint score, and is further strengthened by our results in that individuals with acute chemosensory complaints were more likely to report a change to favorite foods and generate lower quality of life scores than individuals with no complaints or those with mild to moderate chemosensory complaints.

Increased sensitivity to odors emerged as a frequent complaint among patients with advanced cancer. In support of this finding, Pattison et al[24] have provided empirical evidence that patients with advanced cancer experience enhanced olfactory sensation; they determined that patients with advanced cancer demonstrated increased odor discrimination capability relative to age-matched controls.

Specific chemosensory complaints relating to sensitivity to the basic tastes (salty, sour, sweet and bitter) were highly variable; complaints ranged from decreased to increased sensitivity to all basic tastes, and many individuals reported mixed sensitivities to specific basic tastes. Despite this variability, a trend emerged among individuals reporting a change to their sensitivity to bitter (n=12) and/or sour (n=16) stimulus whereby the overwhelming majority described increased sensitivity to these basic tastes. While these specific chemosensory changes have previously been identified in patients with cancer[19,20,25], no other disease state has shown a similar chemosensory profile with these isolated sensory changes; age-related chemosensory changes tend to result in decreased olfactory acuity and decreased sensitivity for all tastants[47]. Increased perception of bitter or sour could be expected to result in 'off flavors' of foods consumed; addressing this relatively consistent finding by using masking agents to neutralize these taste stimuli may be an important strategy to improve food enjoyment and food intake among individuals with abnormal chemosensory perception. That said, the overall variability in subject responses highlights the individuality of abnormal chemosensory perception and emphasizes the need for further chemosensory testing in this population in order to determine the most appropriate strategies to improve energy intake and quality of life related to chemosensory dysfunction.

The observed variation in taste perception may be due in part to the fact that abnormal perception of the basic tastes may be difficult for the patient to isolate; the bitter taste quality seemed to be particularly difficult for subjects to identify. Abnormal sensitivity to a specific taste can be confused with general flavor perception; furthermore, smell complaints are frequently misinterpreted as taste abnormalities due to the central role olfaction plays in flavor perception[7,44,46]. Care was taken to clarify the differences among the basic tastes and to help subjects distinguish between taste and flavor perception during the patient interview in order to minimize patient confusion in this regard. The fact that both increased and decreased sensitivity to basic tastes were reported within the same individual, and the fact that increased odor sensitivity was reported among individuals who also described decreased taste sensitivities suggests that our subjects were sufficiently able to discriminate among the basic tastes, as well as between taste and smell.

Associations between age[47], gender[48], oral health and dentition[49], smoking status[50], number and type of medications taken[7,51], various cancer treatments[15-17] and chemosensory function have been identified in healthy populations and among individuals with various clinical diagnoses such as AIDS[7] and cancer[18-25]. The relatively small sample size limited our ability to explore potential causes of the reported chemosensory dysfunction in our population. Furthermore, though patients with advanced cancer typically experience numerous symptoms that are likely to affect appetite and food intake[33], such as pain, nausea, early satiety, anxiety and depression, we did not have the statistical power to perform multivariate analysis assessing the effect of these clinical factors on food enjoyment and energy intake. Therefore we cannot say if or how the presence of these symptoms would affect the relationship between altered chemosensation and dietary intake. Additional analyses should be conducted with a larger sample providing greater statistical power in order to evaluate their relationships with abnormal chemosensation and dietary intake.

This study demonstrated that a high proportion of patients with advanced cancer experience self-perceived chemosensory dysfunction. The reported changes to taste and smell perception were significantly associated with energy intake, weight loss, food choice, food enjoyment and quality of life. Diagnosis of taste and smell abnormalities is especially important in the palliative care setting, where quality of life and control of distressing symptoms are of utmost priority in patient care. Further research is required to determine potential causes of the reported chemosensory dysfunction, and to identify appropriate strategies to reduce the chemosensory complaints in this population; additional investigations identifying preferred foods and their relationship to chemosensory perception are warranted. Such interventions have the potential to improve energy intake, nutritional status and quality of life.

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CHAPTER SIX

6.0 SUMMARY AND CONCLUSIONS

Malnutrition is recognized as an indicator of poor prognosis and is a source of emotional distress among patients with advanced cancer[1-3]; however, existing practice and investigational strategies targeting the malnutrition of advanced cancer are restricted by the lack of basic dietary knowledge pertaining to this population. Information relating to current nutrient intakes and food preferences, and an increased understanding of the effects of chemosensory symptomology on nutrient intake, are required to develop suitable dietary interventions that optimize nutritional status in patients with advanced cancer. This research project was conducted to increase current knowledge regarding nutrient intakes and dietary habits among patients with advanced cancer, and to examine the relationship between self-perceived chemosensory function, food intake and quality of life in this population.

6.1 DIETARY PATTERNS IN PATIENTS WITH ADVANCED CANCER: MAJOR FINDINGS

Our results suggest that patients with advanced cancer are an heterogeneous group in terms of dietary intake and food choice. Energy intake was normally distributed but showed wide variation, ranging between 4 and 51kcal/kg BW/day with a mean intake of 25 ± 10kcal/kg BW/day (mean ± standard deviation). Similarly, protein intake was widely distributed with a mean of 1.0 ± 0.4g/kg BW/day (range 0.1 to 2.4g/kg BW/day). While energy requirements for this population have not been empirically determined, they are estimated to fall in the range of 26 to 34kcal/kg BW/day; by this estimation, the majority (83%) of individuals in our population were consuming insufficient energy to support weight maintenance and normal functional capacity. The standard protein intake recommended for weight maintenance in patients with cancer, depending on treatment regimen and nutritional status, is between 1.0 to 2.0g protein/kg BW/day[4]; 47% of participants reported a mean protein intake below 1.0g protein/kg BW/day. Individuals with limited dietary variety and food consumption patterns that were highly divergent from typical intake patterns observed in healthy populations of the same age tended to have the lowest energy and protein intakes placing them at increased risk for protein-energy malnutrition.

The studied subjects corresponded to the inclusion criteria of a number of recent large clinical trials of cancer cachexia intervention for which the stated objective is the maintenance or gain of weight and lean body mass[5-17]. Our data suggest that the current diet of patients with advanced malignancy is likely to introduce a large degree of variability in study populations and in the ability of patients to respond to such treatments; the fact that estimated energy and protein intakes are well below estimated requirements makes it less possible or impossible to realize this aim. Orexigenic therapies or nutrient supplementation trials could not be expected to induce weight gain in the lowest intake quartile unless such agents were capable of doubling or tripling intakes to reach levels necessary to develop positive energy and N balance. The heterogeneity and generally poor level of dietary intakes may help to explain observed cachexia treatment failures[10,18]. Our data emphasizes the fact that orexigenic or anabolic therapies must be supported by foods or supplements providing adequate energy and high quality protein to achieve net tissue accretion.

Currently, the majority of nutrition supplements developed or suggested for patients with advanced cancer come in the form of powdered protein products or liquid oral supplements such as Boost® or Ensure®[5,8,9,16]. Our results suggest that though these products are frequently recommended for patients with advanced cancer, they may not be the ideal medium for nutrient supplementation in patients with advanced cancer as they are not selected by a large fraction (70%) of patients sampled; supplementation with this type of product would not only introduce a food product not otherwise selected by the majority of patients, but would likely displace a large fraction of 'normal' food intake[19]. Other forms of nutrient supplementation may be worthy of exploration, such as nutrient augmentation of foods that are habitually consumed.

Previous research has shown that food acceptance by cancer patients is improved when personal tastes and eating habits are considered[20,21]. For the studied population, meats, desserts, fruit, white bread and milk provided the bulk of dietary energy. The population stratified into 3 distinct dietary patterns that were determinants of energy and protein intake; milk, meat and fruit provided the greatest division among the three patterns of dietary intake while desserts were a popular food choice among most participants.

The capacity for intake at any given meal appeared to be limited and therefore the frequency of eating (number of meals or snacks consumed per day) emerged as an important variable in total energy intake. The positive relationship between number of eating episodes and caloric intake was largely derived from the consumption of food outside of the 3 main meals of the day. These results support the use of high nutritional value snacks for improvement of protein and energy intakes in patients with advanced cancer; based on the food choices observed, a dessert-type snack product may prove to be an effective vehicle for nutrient supplementation in this population.

6.2 SELF-PERCEIVED CHEMOSENSORY ABNORMALITIES AND DIETARY INTAKE IN PATIENTS: MAJOR FINDINGS

Decreased appetite resulting in inadequate dietary intake is a significant factor involved in the weight loss and progressive functional decline associated with advanced cancer; the anorexia associated with malignancy may be related in part to changes in chemosensory perception. Our results indicate that a significant proportion of individuals with advanced cancer experience altered chemosensory function, such that sensitivity for specific odors and tastants may be increased and/or decreased. Eighty-six percent (95% CI, 76-96%) of subjects reported some type of subjective chemosensory abnormality and 50% (95% CI, 36-64%) described changes to both taste and smell perception. Though it cannot be stated whether the reported abnormalities in chemosensory perception resulted in or are simply an indicator of decreased dietary intake, the observed relationship between chemosensory complaints and energy intake in patients with advanced cancer provides evidence that those reporting self-perceived chemosensory disturbances are at increased risk for malnutrition.

DeWys[22] associated decreased dietary intake with chemosensory distortion in a group of cancer patients; the author suggested that the observed decline in dietary intake in a group of cancer patients is related to a decreased hedonic value of foods and a disruption of normal physiological responses to food caused by abnormal chemosensation. Studies in elderly populations[23] have shown that nutrition interventions designed to increase the palatability of foods for chemosensory impaired individuals improves dietary intake, food enjoyment and functional status. Furthermore, the observed relationship between chemosensory complaint score and dietary intake pattern supports the notion that altered chemosensory function is likely to affect food preferences and dietary habits. These combined results suggest that dietary interventions catering to the unique chemosensory symptomology of patients with advanced cancer may result in improved dietary intake and therefore warrant further investigation. Indeed, anti-cachexia therapies such as orexigenic agents may not be sufficient to overcome chemosensory abnormalities and improve dietary intakes in patients affected by this symptom unless such interventions incorporated dietary strategies addressing altered chemosensory perception.

The variability in subject descriptions of perceived chemosensory dysfunction highlights the individuality of abnormal chemosensory perception and emphasizes the need for further chemosensory testing in this population. Comprehensive studies using reliable up-to-date techniques are required to further investigate the nature of chemosensory disruption in patients with advanced cancer; additional research is required to determine potential causes of the reported chemosensory dysfunction if appropriate strategies to reduce the chemosensory complaints in this population are to be identified.

Food enjoyment was significantly lower among individuals reporting acute chemosensory dysfunction, as was global quality of life. As the goal of palliative care is the minimization of symptom distress and maintenance of patient quality of life, palliation of the distressing and nutritionally disruptive symptom of chemosensory distortion should receive increased attention. Attempts to improve or normalize the chemosensory experience of terminal cancer patients have the potential to improve energy intake, nutritional status and quality of life.

6.3 Final Comments

The results presented provide a basis for understanding current food selection, nutrient intake and future dietary supplementation in patients with advanced cancer. While the variability in dietary intakes, food preferences and self-perceived chemosensory abnormalities in this population supports individualized dietary assessments and interventions, the identified dietary patterns may help in the development of specific recommendations for overall dietary improvement. Furthermore, these results facilitate the identification of foods that might be well accepted by the population as vehicles for nutrient supplementation. This study is the first to investigate the effects of self-perceived chemosensory abnormalities on dietary intake, food enjoyment and quality of life among patients with advanced cancer who are not receiving active radiation therapy or chemotherapy. Our results highlight the importance of food beyond the simple provision of nutrients; perceived chemosensory distortions and their effects on food enjoyment can have a profound impact on quality of life.

At present, dietary interventions and anti-cachexia strategies for patients with advanced cancer are not framed within the context of the current food and nutrient intake, food preferences, and sensory symptomology of this patient group; this is the first study to investigate and describe the relationship among these variables in this population. Future research relating to anti-cachexia nutritional therapies must incorporate these key factors in order to develop improved methods for addressing the nutritional status and quality of life in patients with advanced cancer.

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APPENDIX A

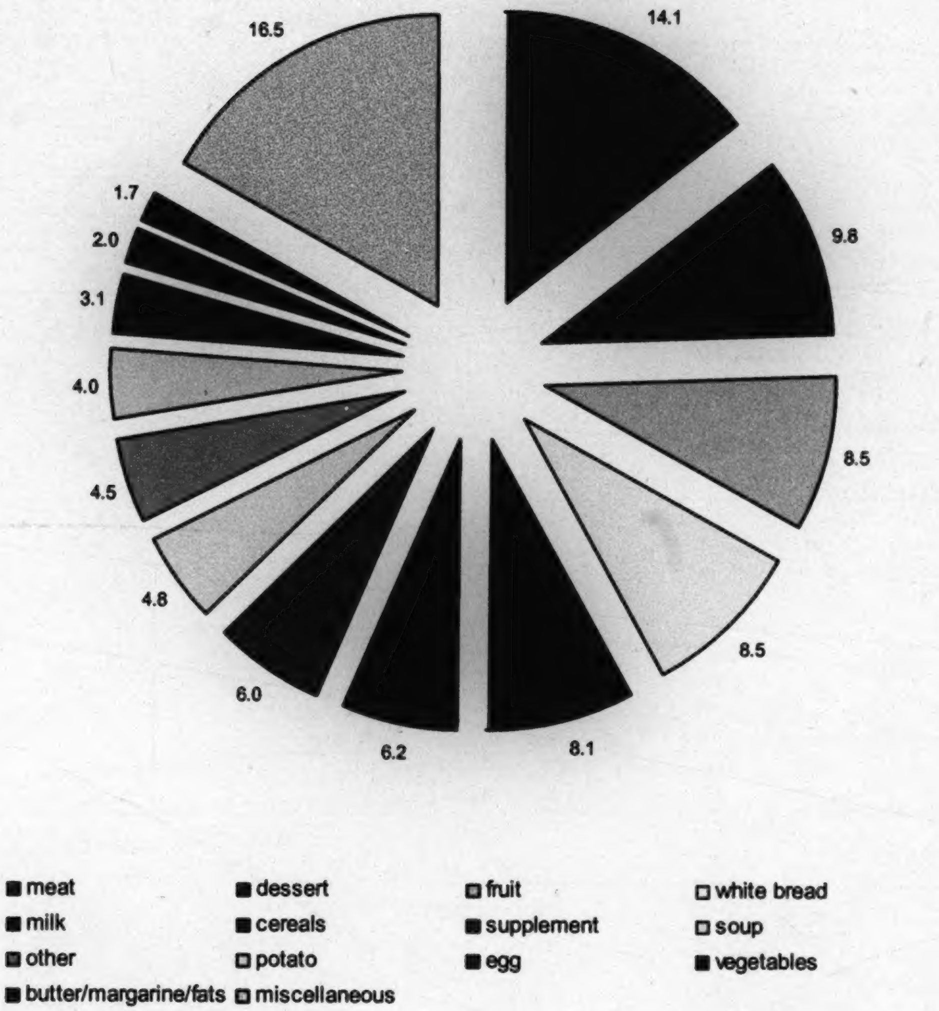

Figure A.1 Distribution of % total energy contribution by food category for the study population.

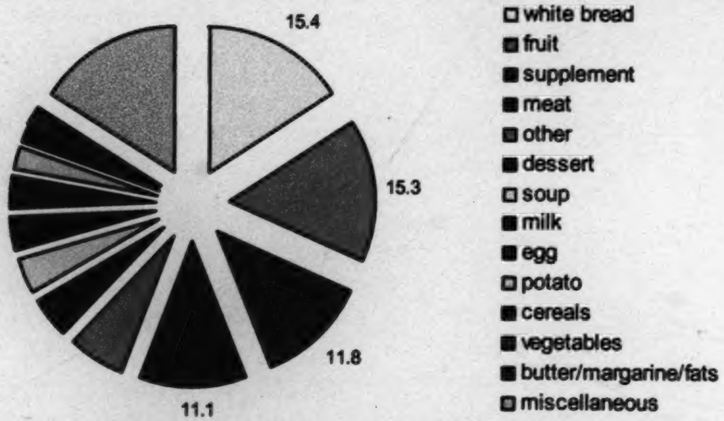

Figure A.2 Distribution of % total energy contribution by food category for the "Milk & Soup Liquid" Dietary Pattern.

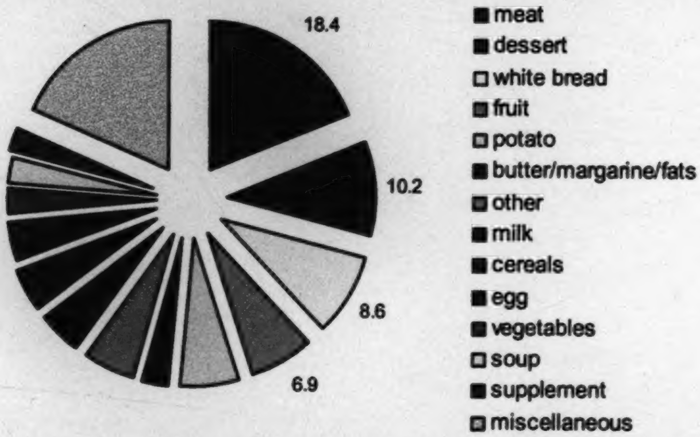

Figure A.3 Distribution of % total energy contribution by food category for the "Fruit & White Bread" Dietary Pattern.

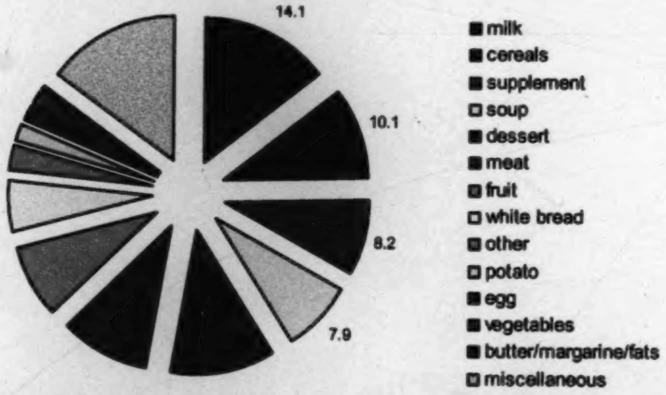

Figure A.4 Distribution of % total energy contribution by food category for the "Traditional Meat & Potato" Dietary Pattern.

APPENDIX B

Survey Tools:

Taste and Smell in Cancer Patients Part 1

Taste and Smell in Cancer Patients Part 2 (Targeted Interview)

Functional Assessment of Anorexia-Cachexia Therapy (FAACT) Quality of Life Questionnaire

TASTE AND SMELL PERCEPTION IN CANCER PATIENTS

(Part 1)

The purpose of this survey is to see how cancer affects the senses of taste and smell. Please answer the following questions as best you can.

Participant Number: ______________________ Date: ___/___/___

1. Have you noticed any changes in your sense of taste? yes no

   If yes, please describe: ____

   ____

2. Have you noticed any changes in your sense of smell: yes no

   If yes, please describe: ____

3. Have you ever noticed that a food tastes different than it used to? yes no

   If yes, please describe: ____

4. Have you ever noticed that a food smells different than it used to? yes no

   If yes, please describe: ____

5. I have a persistent bad taste in my mouth (circle BEST answer)

   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent taste is (circle ALL that apply)

   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (please specify) ______________________________

7. Do specific drugs interfere with your sense of taste? yes no

If yes, which ones? ____

8. Do some drugs taste worse than others? yes no

If yes, which ones? ____

9. Do specific drugs interfere with your sense of smell? yes no

If yes, which ones? ____

10. Do some drugs smell worse than others? yes no

If yes, which ones? ____

11. Comparing my sense of taste now to the way it was before I was diagnosed with cancer:

a. Salt tastes (circle BEST answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

b. Sweet (sugar) tastes (circle BEST answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

c. Sour (lemon) tastes (circle BEST answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (circle BEST answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

12. Comparing my sense of smell not to the way it was before I was diagnosed with cancer, odors are

1) stronger
2) as strong
3) weaker
4) I cannot smell at all

13. Over the past 3 months, I would rate my abnormal sense of taste as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

14. How has your abnormal sense of taste affected your quality of life?

____

15. Over the past 3 months, I would rate my abnormal sense of smell as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

16. How has your abnormal sense of smell affected your quality of life?

____

TASTE AND SMELL PERCEPTION IN CANCER PATIENTS

(PART 2)

(To be administered by the research assistant)

There are 3 short sections to this survey.

The purpose of this part of the survey is to determine if there are factors other than cancer that influence your sense of taste and smell. Please answer the following questions as best you can.

1.	Are you a cigarette smoker? (If yes, proceed to question 3)	Yes	No
2.	If you are not a current smoker, are you a former cigarette smoker?	Yes	No
3.	Do you wear dentures?	Yes	No
4.	Have you had mouth and/or gum infections in the past two years?	Yes	No
5.	Are you currently bothered by hay fever and/or allergies? sinusitis?	Yes	No
6.	Are you currently bothered by sinusitis?	Yes	No
7.	Does your sense of smell change from day to day?	Yes	No
8.	Does your sense of taste change from day to day?	Yes	No
9.	Has a doctor previously diagnosed you with any taste or smell problems?	Yes	No
10.	Before your cancer, did you have any problems with your sense of taste or smell?	Yes	No
11.	Do you smell "phantom odours"? (you can smell something but the source of the smell is nowhere near you)	Yes	No

Some symptoms or problems can affect your ability to eat. Please indicate the extent to which you experienced these symptoms or problems in the past week, using a scale from **one** to **five**, where **1** represents "not at all" and **5** represents "very often".

	Not at all				Very often
12. Do you have pain or soreness in your mouth?	1	2	3	4	5
13. Do you have pain in your jaw?	1	2	3	4	5
14. Do you have pain in your throat?	1	2	3	4	5
15. Do you have problems swallowing liquids?	1	2	3	4	5
16. Do you have problems swallowing pureed foods?	1	2	3	4	5
17. Do you have problems swallowing solid food?	1	2	3	4	5
18. Do you have a dry mouth?	1	2	3	4	5
19. Do you have sticky saliva?	1	2	3	4	5
20. Do you have trouble eating?	1	2	3	4	5
21. Do you enjoy your meals?	1	2	3	4	5
22. Do you feel hungry at mealtime?	1	2	3	4	5

This part of the survey asks about your favourite foods. If you do not have any favourite foods, that's ok.

23. Before you were diagnosed with cancer, what were three of your favourite foods?

____

____

____

24. Currently, what are three of your favourite foods?

____

____

____

25. Many people say they have 'good' and 'bad' days. Are the foods that you like to eat on 'good' days different from the foods you like to eat on 'bad' days?

Yes No

26. What are three foods or beverages that you like to eat or drink on a 'good' day?

____

____

____

27. What are three foods or beverages that you like to eat or drink on a 'bad' day?

____

____

____

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	[illegible]	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FAACT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

US English

FAACT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C6	I have a good appetite	0	1	2	3	4
ACT 1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT 2	I am worried about my weight	0	1	2	3	4
ACT 3	Most food tastes unpleasant to me	0	1	2	3	4
ACT 4	I am concerned about how thin I look	0	1	2	3	4
ACT 6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT 7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT 9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT 10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT 11	I have pain in my stomach area	0	1	2	3	4
ACT 13	My general health is improving	0	1	2	3	4